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FURTHER EXPERIENCE WITH PERCUTANEOUS LIENO-PORTAL VENOGRAPHY

by

V. Gvozdanović and *E. Hauptmann*

When we completed our first paper on percutaneous lieno-portal venography (PLPV) one and a half years ago, our material comprised 14 cases, while our conclusions on the value of the method were based on our own experiences as well as on the paper by Dreyer and Budtz-Olsen. To-day, the literature on this method is much richer and includes articles published before ours, and which were not accessible to us at the time. Our experiences and further observations based on 61 examinations may therefore now be compared with the results obtained by other authors, and the advantages and dangers of PLPV evaluated in a more objective manner.

History

In our first paper we stated that Abeatici and Campi were the first to perform experimental PLPV in the dog while Dreyer and Budtz-Olsen were the first to apply the procedure in man. It is probable that they also considered this to be the case, for they do not quote other authors. As we learned later, in April 1951, de Sousa Pereira published a case in which he had succeeded in showing the splenic vein by a transparietal injection of a contrast medium into one of the veins in the splenic hilus. In May 1951 Leger et al. described lieno-portal venographies performed by injecting a contrast medium into the splenic parenchyma at operation, while in September of that year the same author and his co-workers published the transparietal method of injecting a contrast medium into the spleen.

However, in April, 1953, Bahnson et al. stated that, as early as 1942, they had succeeded quite by chance in introducing iodochloral into the portal system of a patient with abscesses in the abdomen and liver. In 1949, they had commenced experiments in dogs and the same year had carried out successful PLPV in human subjects.

Terminology

The terminology employed by the various authors for the method is not uniform. While Abeatici and Campi are concerned with 'hepatic angiography', other authors, such as Boulvin et al., Leger et al., Milnes-Walker et al., and Fuld and Irwin,

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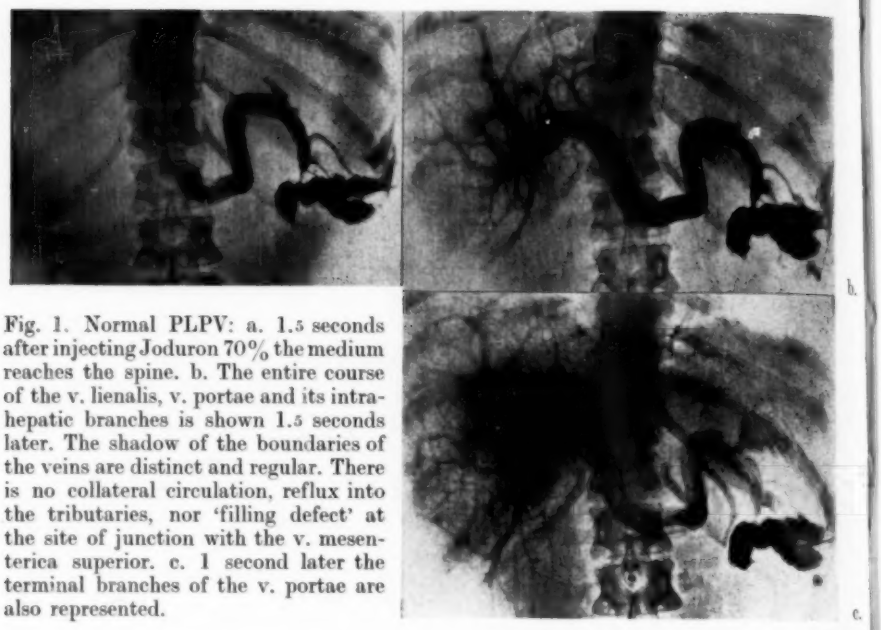


Fig. 1. Normal PLPV: a. 1.5 seconds after injecting Joduron 70% the medium reaches the spine. b. The entire course of the v. lienalis, v. portae and its intra-hepatic branches is shown 1.5 seconds later. The shadow of the boundaries of the veins are distinct and regular. There is no collateral circulation, reflux into the tributaries, nor 'filling defect' at the site of junction with the v. mesenterica superior. c. 1 second later the terminal branches of the v. portae are also represented.

write about 'portography' or 'portal phlebography'. DREYER and BUDTZ-OLSEN, and KONOR and SEN GUPTA, on the other hand, speak of 'splenic venography'. SOTGIU et al., in an endeavour to combine these two conceptions, use the term 'spleno-portography'. This term was also adopted by LEGER who has used it lately, and the same may be said of COOPER and his co-workers. We would like to stress, however, that we are not concerned here with a representation of the spleen or the liver. The method is employed to show the vena lienalis and vena portae with its intra-hepatic ramifications (Fig. 1 a—c) and we therefore propose the term 'percutaneous lieno-portal venography (PLPV)'. The word 'percutaneous' is included as the method is performed percutaneously, and not at operation with the abdomen exposed.

Technique

We adhered, on the whole, to the technique described in our first paper. One hour after the administration of a sedative, the patient was placed on the roentgen table in the supine position and a local anaesthetic, consisting of 1 % novocaine, injected into the eighth, ninth or tenth intercostal space in the anterior-axillary line. Experience having shown that it was difficult to pass the puncture needle into the abdominal cavity through the skin without causing sudden movements on the part of the patient, we made a skin incision prior to the puncture. In so doing, we facilitated the introduction of the needle through the chest wall. The point of the needle having reached the surface of the spleen — which was established by a sensation of scratching, — the patient was told to take a deep breath. The needle was then pushed 2 to 3 cm into the spleen, and

the contrast medium injected. In all our examinations Joduron 70 % was used, 20 ml of which were injected in 2 to 3 seconds.

Of late, we have altered the roentgenographic technique. While formerly we worked with the ordinary roentgen table and changed the cassettes by hand, the last 7 venographies were performed with the Elema film-changing apparatus, which makes it possible to expose up to 4 films per second. The factors were 400 mA, 70 to 80 kV, F. F. D. 95 cm and 0.1 second. We used a fine cross-grid and a Super-Dynamax tube. Two films a second during 7 to 14 seconds were taken. By the use of the above apparatus it is possible to watch accurately the passage of the contrast medium through the blood vessels, and in this manner to establish the speed of the lieno-portal circulation in various conditions.

An intravenous test is carried out before the procedure in order to reveal any sensitivity to iodine, while after the procedure the patient is advised to rest for 24 hours.

Material

Up to the present we have performed 61 PLPVs in 54 patients (Table 1); in some patients the examination was performed twice. As it was not merely our aim to discover pathologic conditions along the course of the vv. lienalis and portae, PLPV was also performed in cases with spleno-megaly, in which a normal finding was expected in the vessels under discussion. The reason for this lies in the fact that the literature contains scanty descriptions of the normal course of the vv. lienalis and portae by the use of this method; we considered spleno-megaly the only indication for its exhibition, naturally after a haemor-

Table 1

Material

Number of cases Diagnosis	61 PLPVs on 54 patients Number	
Subacute bacterial endocarditis	1	
Tuberculosis of the spleen	1	
Polycytemia	1	
Hereditary spherocytosis	8	(7)*
Osteosclerosis	1	
Chronic myeloid leukemia	5	
Boeck-Schaumann's disease	1	
Brill-Symmer's disease	1	
Hodgkin's disease	1	
Reticular sarcoma	2	(1)
Lymphosarcoma, Chronic lymphoid leukemia	7	(6)
Splenomegaly of unknown origin	10	(9)
Hepatic cirrhosis	12	
Wilson's disease	1	
Thrombosis of the v. lienalis	9	(6)
	Total 61	(54) PLPVs

* The figure in parenthesis expresses the number of patients on whom PLPV was performed.

rhagic diathesis had been excluded. Accordingly, PLPV was performed in cases of systemic diseases, osteosclerosis, endocarditis lenta etc., and not only in those in which on clinical grounds we suspected thrombosis or hypertension in the portal system.

In the material presented, PLPV was successfully employed 55 times, while in 6 cases it was not possible to represent the lieno-portal system of veins or the collateral circulation. The reason for this was the supervention of complications which are sometimes associated with the method.

Side reactions and complications

Symptoms following PLPV are so typical as to indicate that the procedure has been successful. They are:

a sensation of heat — especially in the head, nausea, and pain in the punctured area. All these symptoms are of a transitory character and of short duration. The sensation of heat appears immediately after the contrast medium has been injected, or even during the actual injection, and is sometimes accompanied by reddening of the face; it disappears after 1 to 3 minutes. Nausea, too, is of short duration; it occurs a little later than the sensation of heat and lasts about 5 minutes. Pain at the site of puncture, that is to say, in the region of the left costal margin, is somewhat prolonged. It usually vanishes only after 12 to 24 hours.

Besides these phenomena, which are harmless and do not produce major disturbances to the patient, PLPV may also cause complications. We are thinking in the first place of the spread of the contrast medium backwards along the puncture canal, and its distribution between the splenic capsule and the surrounding organs. This occurs when, owing to the puncture being too shallow, the contrast medium has been injected superficially. This outflow of the contrast agent produces pain under the left costal margin, which often spreads to the left shoulder. In our material, this could be observed in 10 cases (Table 2).

Table 2

Complications

Spread of the contrast medium backwards along the puncture canal	10 ×
Medium injected into the peritoneal cavity	2 ×
Medium injected into the stomach	2 ×
Medium injected into the colon	2 ×
Bleeding from the spleen	2 ×
Total	18 ×

It may also happen that the contrast medium is injected into the peritoneal cavity or into another organ situated in the abdomen, apart

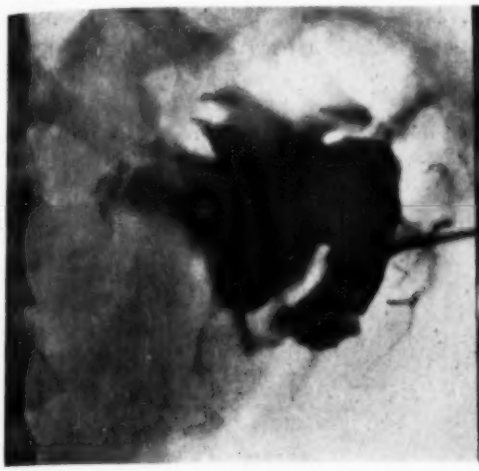


Fig. 2.

Fig. 3.

Fig. 2. Contrast medium injected into the stomach.

Fig. 3. The needle has been pushed through the spleen and the medium injected into the abdominal cavity between the spleen and stomach wall.

from the spleen. In either case there is no sensation of heat, but a moderate degree of pain and rather pronounced nausea. The injection of the contrast medium into the stomach (Fig. 2) produces the most pronounced nausea observed by us when using this method, sometimes accompanied by vomiting. In our material, this happened on two occasions on both of which the contrast medium was introduced into the stomach through the spleen owing to the puncture being too deep. In two cases the contrast medium was injected into the peritoneal cavity (Fig. 3). The injection was accompanied by moderate pain, but without any other secondary manifestations. On two occasions the contrast medium was injected into the colon, but without producing symptoms (Fig. 4 a—b).

Bleeding from the spleen is probably a normal feature when performing PLPV, excepting when it is so marked as to cause symptoms. This is evident from the fact that the abdominal cavity of patients operated on a few hours after PLPV contained some blood. Only one patient experienced pain in the abdominal cavity caused by bleeding, and for 24 hours the abdomen was diffusely sensitive. There was one case of cirrhosis, which showed profuse bleeding, during which the patient, a woman, collapsed; she recovered after a copious blood transfusion.

a. b.

Fig. 4. a. Contrast medium injected into the colon. b. None can be seen one hour later at this site; it appeared in the renal pelves.

Results

The first and foremost question to be raised when investigating this insufficiently explored field of radiologic diagnostics, is: Where does the boundary between the normal and the pathologic lie? Despite our 61 examinations, it is not easy to give an answer to this question for the simple reason that — like the majority of other authors — we performed PLPV only in cases of an enlarged spleen, that is, in cases in which the organ itself into which the contrast medium was injected showed pathologic changes. Thus, when speaking of the 'normal finding', this is always a relative concept for we assume that the spleen is enlarged but that there are no essential changes of the circulation either in this organ, or in the lieno-portal system of blood vessels.

On the basis of our present experiences, we consider that the series of films in Fig. 1 a—c should be taken as the prototype of the 'normal finding' in view of the position, course, and calibre of the vena lienalis

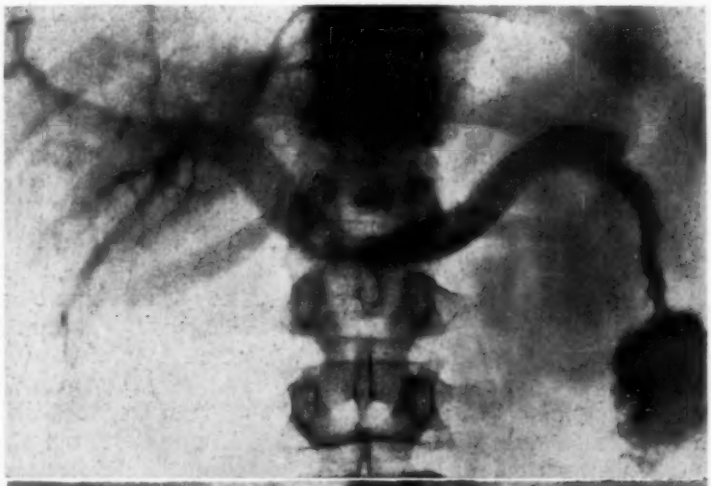


Fig. 5.

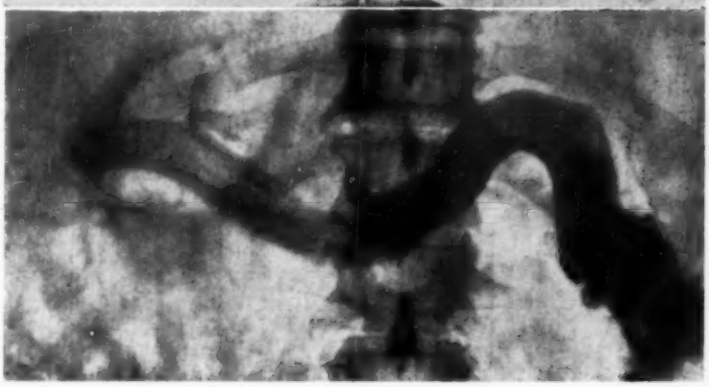


Fig. 6.

Fig. 5. A high-situated and rather narrow splenic vein.
Fig. 6. Wide v. lienalis and v. portae without collateral circulation and/or reflux in their tributaries.

and vena portae, and the ramification in the liver, as well as absence of collateral circulation. This series of films at the same time confirms the assumption in our previous publication of the importance of serial roentgenography in PLPV. From the film of Fig. 1 a alone, an erroneous diagnosis of obstruction of the vena lienalis might readily be made.

The width of the vv. lienalis and portae is markedly varied. From a relatively narrow calibre (Fig. 5) to a pronounced enlargement (Fig. 6) we may find all possible transitions. By measuring the width of the vv.

lienalis and portae in 40 PLPVs, an average value of 1.6 cm for the v. lienalis and 1.9 cm for the v. portae, was obtained; the width of the v. lienalis, however, varied between 1.3 and 3 cm, and that of the vena portae between 1.5 and 3 cm. In cases of cirrhosis we mostly found a somewhat enlarged lumen; more rarely it was normal but it was never narrowed. Expressed in figures, the average width of the v. lienalis was 1.8 cm, of the v. portae 2.1 cm, with variations of 1.3 to 3 cm and 1.8 to 3 cm, respectively (measured in 11 cases of cirrhosis). If we compare these values with the average width of the same veins in hereditary spherocytosis (v. lienalis 1.5 cm, v. portae 1.7 cm — measured in 7 cases), which we may consider as having a normal lumen, we shall see that the average width of the v. lienalis in cirrhosis is 3 mm greater than normal, and of the v. portae, 4 mm. A large lumen of the v. lienalis and portae was found also in individual cases of leukaemia (1.8 and 2.2 cm resp.), lymphosarcoma (2.5 and 2.5 cm resp.), endocarditis lenta (1.8 and 2.2 cm resp.), and in splenomegaly of unknown origin (2 and 2 cm resp.), in which cases there were no functional disturbances of the liver parenchyma. To generalize, the lumina of the v. lienalis and v. portae in PLPV are on an average a little wider than we should expect from the anatomic text-books.

The position and course of the vv. lienalis and portae are dependent on the size and position of the spleen, left kidney, pancreas, and liver. In our material, we found all transitions from a high-situated, almost straight vv. lienalis and portae (Fig. 7) to a low-placed v. lienalis, tortuous in the vertical plane (Fig. 8). A markedly tortuous course was likewise found to be present in lymphosarcoma and myeloid leukaemia with a normal lieno-portal circulation, as well as in individual cases of cirrhosis. But there were also cases of cirrhosis with an almost straight course of the vv. lienalis and portae (Fig. 7).

By analyzing 47 PLPVs we were able to establish that in 34 cases the v. lienalis passed over the vertebral column at the level of the first lumbar vertebra. The upper boundary of the position of the v. lienalis in our material was at the level of the 12th thoracic vertebra, and the lower boundary at the level of the 3rd lumbar vertebra.

The angle formed by the v. portae and the vertebral column — measured in 47 PLPVs — yielded an average value of 45°, with extreme values of 20° and 90°. The average value in cirrhosis (measured in 11 PLPVs) was 46°, with extremes of 30° and 80°. The greatest variations were found in splenomegalia e causa ignota — 20° to 90° (measured in 7 cases).

The ramification in the liver is greatly dependent on the size of the lobes. While the representation of the right branch in normal cases is

Fig. 7.

Fig. 8.

Fig. 7. The collateral circulation is performed through the dilated v. coronaria ventriculi in this case of commencing portal hypertension (hepatic cirrhosis). The course of the v. lienalis and v. portae is almost linear.

Fig. 8. Vertically situated, tortuous splenic vein of medium size.

good, the left branch is often more poorly represented (Figs. 5 and 7). It is usually short, which is in part caused by its projection (Fig. 1 b). We rarely encountered a long left branch of the v. portae (Fig. 9). The pathologic changes in the ramification may be demonstrated with certainty only by means of rapid roentgenography.

The speed of the circulation in the lieno-portal system can be accurately established only by serial roentgenography, together with automatic transportation of the film. This technique, in two planes, was

Fig. 9.

Fig. 10.

Fig. 9. A well-represented and long left branch of the portal vein.

Fig. 10. Very wide v. lienalis and v. portae in a case of hepatic cirrhosis. The collateral circulation is performed through the vv. gastricae breves and the v. coronaria ventriculi. The ramification of the v. portae is poor (but the film may have been taken prematurely).

utilized by TORI and SCOTT in PLPVs made in dogs. In our material, we used this technique in 7 examinations. Among these, there were two cases of hereditary spherocytosis, and one case of chronic myelosis. None of these 3 cases showed clinically changes within the circulation. By carrying out the roentgenography at a rate of two films per second,

we obtained in all these three cases the following results (the times were reckoned from the moment of the commencement of the injection of the contrast agent):

0.5 sec.: The contrast medium enters the proximal part of the v. lienalis.

1 sec.: The medium enters the v. lienalis up to the region where it passes over the vertebral column.

1.5 sec.: The medium fills the v. portae up to its ramification.

2 sec.: The ramification begins to fill.

2.5 sec.: The contrast medium enters the main branches of the v. portae.

3 sec.: The main branches are represented in their full length.

4 sec.: Representation of the whole of the vv. lienalis and portae as well as of the ramifications up to the terminal branches. The central parts around the hilum are diffusely shadowed in the sense of a capillary phase.

5 sec.: The parenchyma becomes more and more dense, while the density of the contrast medium in the v. lienalis and portae drops.

5.5—6.5 sec.: The parenchyma becomes even more dense while the faintly outlined branches of the v. portae disappear within the shadow of the hepatogram. The contrast medium in the v. lienalis and portae is scarcely visible.

These results were obtained by injecting 20 ml of contrast medium in approximately 2 to 3 seconds. The same technique of roentgenography was applied in a case of severe hepatic cirrhosis with ascites, in which we were able to establish a marked slowing down of the circulation through the liver — the terminal branches of the v. portae appeared only 6 seconds after the commencement of the injection and the hepatogram only 6 seconds later. In this case as well as in those PLPVs performed in cirrhosis which were technically a success, we could not establish any weaker representation of the ramifications of the v. portae in the liver, in spite of pronounced shrivelling of the parenchyma. On the contrary, we gained the impression that a slowing down of the circulation in the liver favoured the representation of these ramifications.

In none of the normal cases could we find a *reflux* of the contrast medium into the tributaries of the vv. lienalis and portae by representing the collateral circulation through anatomically pre-existing anastomoses, while it could be established 6 times in clinically manifest cases of cirrhosis as well as in 5 of the 6 cases of thrombosis of the splenic

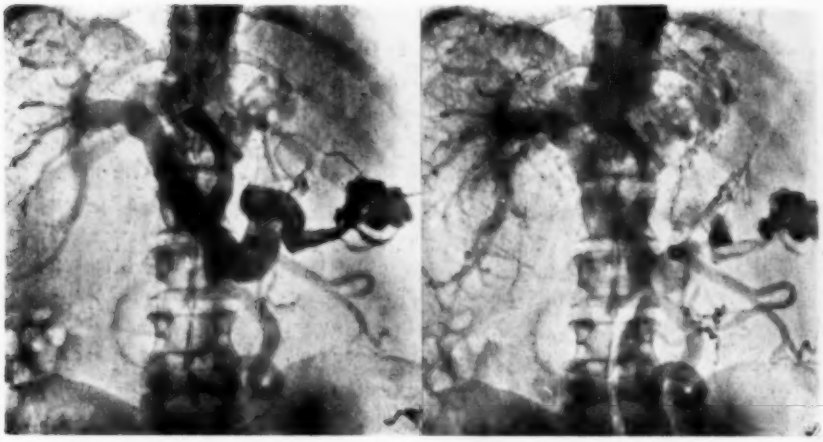


Fig. 11. Abundant reflux into the dilated v. mesenterica superior and inferior, collateral circulation through the vv. gastricae breves and large-sized v. coronaria ventriculi. The v. lienalis and v. portae are dilated and there are varicosities along the veins of the cardia and oesophagus. The intrahepatic branches of the v. portae are well represented in spite of marked liver cirrhosis. This is a typical finding in portal hypertension of intrahepatic origin (hepatic cirrhosis).

vein. The reflux was strongest in the vena coronaria ventriculi (Figs. 7, 10, 11) and in the vv. gastricae breves (Figs. 10, 11). In two cases a collateral circulation through the persistent umbilical vein was found (Fig. 15 a—c).

In all the 6 cases of thrombosis and in one case of cirrhosis, a collateral circulation through newly-formed blood vessels which appear in adhesions was clearly visible. Such vessels were never demonstrated in normal cases. In one case of severe cirrhosis (Fig. 11 a—b), we found an unusually abundant reflux into the tributaries of the vv. lienalis and portae as well as a rich collateral circulation by way of the vv. gastricae breves and v. coronaria ventriculi. The permeability of the vv. lienalis and portae together with a clear representation of the ramification in the liver speak in favour of intra-hepatic genesis in this portal hypertension.

In order to differentiate between portal hypertension of intra- and extra-hepatic genesis, it is necessary, in addition to representing the reflux and collateral circulation through the pre-existing and newly-formed network of blood vessels, to show the actual site of obstruction of the v. lienalis or v. portae, or to demonstrate that the contrast medium does not enter the v. lienalis in spite of a technically correct procedure. There were 6 cases of thrombosis of the v. linealis in our material. It

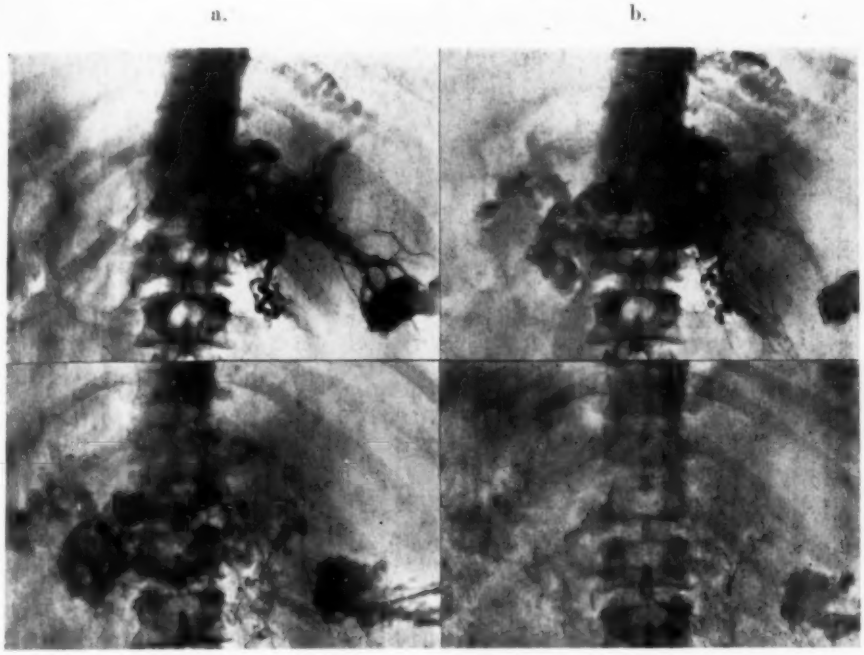
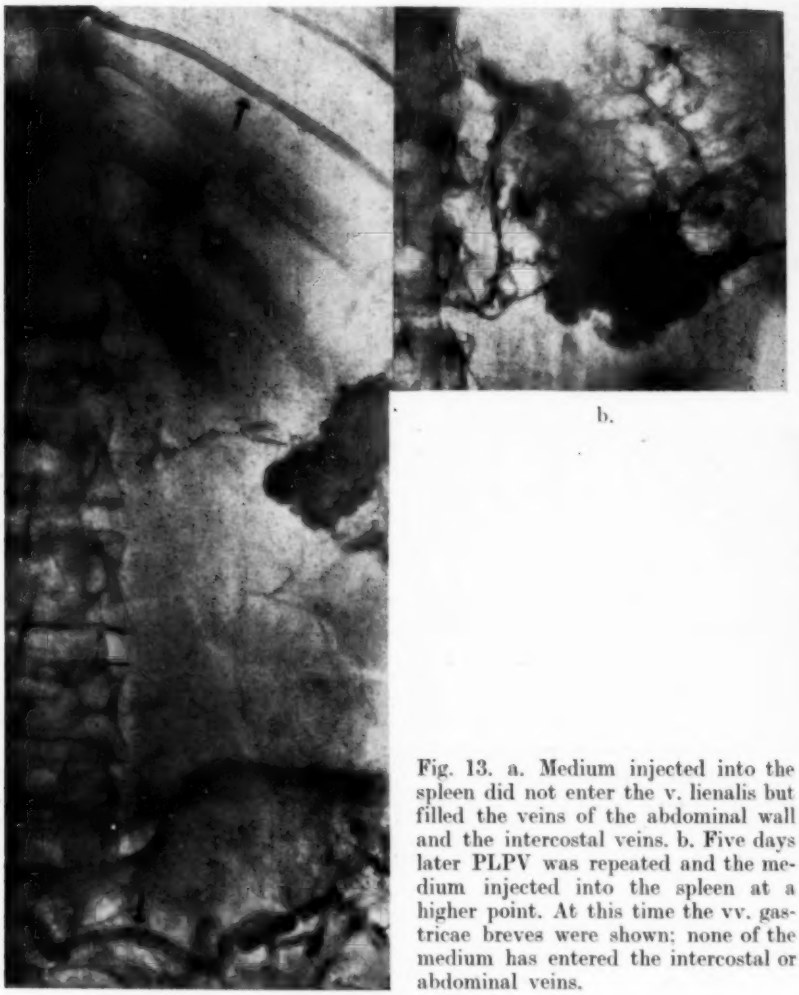


Fig. 12. a—b. Medium injected into the spleen takes two directions: one part flows through the dilated vv. gastricae breves into the veins of the cardia and oesophagus. the other enters the varicose plexus between spleen and liver. c—d. The medium through the vv. gastricae breves disappears after 6 seconds but stagnates, however, in the plexus and reaches the liver 6 seconds later. The v. lienalis is completely thrombosed.

was possible to diagnose the condition by PLPV in all of them. In one of these cases we succeeded in visualizing an extensive varicose plexus between the spleen and the liver, through which the contrast medium emptied into the latter in spite of thrombosis of the v. lienalis (Fig. 12 a—d). The majority of the circulation was effectuated in this case through the vv. gastricae breves into the veins of the cardia and oesophagus. In the second case (Fig. 13 a—b) the medium injected into the spleen did not enter the v. lienalis, but instead appeared in the veins of the abdominal wall as well as in the intercostal veins. On the basis of this occurrence, we were able to draw the valuable pre-operative conclusion that, in addition to thrombosis of the v. lienalis, extensive adhesions between the spleen and the abdominal wall or the diaphragm, or both, existed.

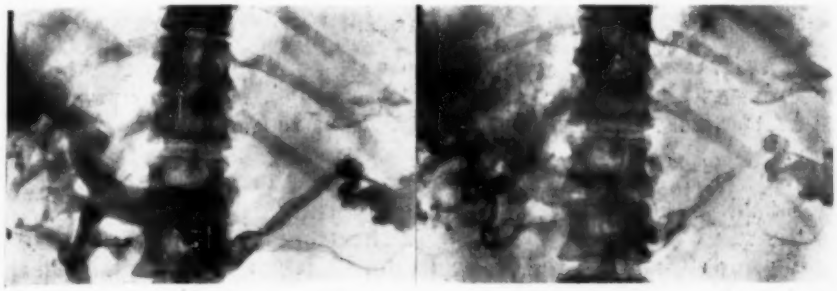


b.

a.

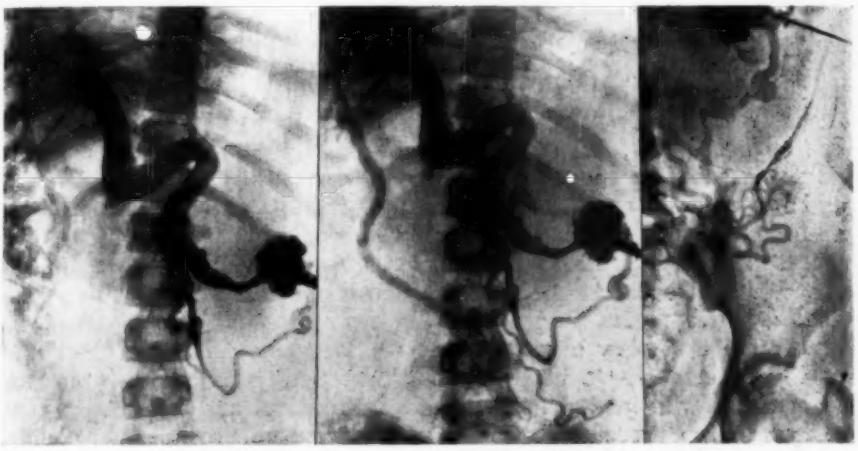
Fig. 13. a. Medium injected into the spleen did not enter the v. lienalis but filled the veins of the abdominal wall and the intercostal veins. b. Five days later PLPV was repeated and the medium injected into the spleen at a higher point. At this time the vv. gastricae breves were shown; none of the medium has entered the intercostal or abdominal veins.

We succeeded in visualizing *anomalies* of the blood vessels in the lieno-portal circulation in three cases. In one case of splenomegaly of unknown aetiology we found a cavernoma in the liver (Fig. 14 a—b). In two cases we were successful in visualizing the persisting umbilical vein (M. Cruveilhier-Baumgarten). In one of our cases it passed from



a. b.

Fig. 14. Hepatic cavernoma. a. Early filling phase. b. Late filling phase.



a. b. c.

Fig. 15. a. The v. lienalis and v. portae are patent. A wide vein directed caudally and medially comes from the left branch of the portal vein. b. 2 seconds later, this vein turns several times close to the umbilicus and continues down to the pelvis. c. The vein ends into the v. epigastrica superficialis, and in this way the medium enters the v. iliaca externa.

the left branch of the v. portae in a caudal—medial direction, was tortuous in the vicinity of the umbilicus, flowed into the v. epigastrica superficialis and by way of the latter into the v. iliaca externa (Fig. 15 a—c), that is to say, into the system of the v. cava inferior.

Discussion

From the available literature we were able to establish that up to the present about 250 PLPVs have been carried out, inclusive of the 61 PLPVs performed by ourselves. According to the present publications, the largest number of PLPVs were performed by LEGER et al. and FULD and IRWIN, *i. e.* 50 by each. A comparison of the results of the individual authors is rendered somewhat more difficult because of the different techniques used. The majority of authors obtained only 2 to 3 films during, or subsequent to, the injection. Under such circumstances, the data on the speed and direction of the circulation, as well as on the nature of the ramification of the v. portae, are exceedingly unreliable, and a comparison of the findings without details of the exposure timing, impossible.

As to the puncture techniques used, appreciable discrepancies between the Franco-Belgian and Anglo-American groups exist. It is true that BAHNSON et al. state that 'frequently, but not always' it is possible to aspirate blood on puncture as evidence that the needle has reached the pulp but it appears that they do not leave the needle in the spleen for any period. A similar technique is utilized by DREYER and BUDTZ-OLSEN, MILNES WALKER et al. (who state that they usually do not obtain any blood by aspiration), KONOR and SEN GUPTA, FULD and IRWIN, and COOPER et al. In contrast, LEGER et al., BOULVIN et al., and DE SCOVILLE and LEROUX leave the needle in the spleen for a prolonged period. They first inject a small amount of contrast medium into the spleen in order to see whether it collects around the point of the needle, which means that the needle lies in the pulp. BOULVIN et al. even state that they observe with a diascope movement of the needle during respiration. On the other hand, we performed all our punctures on patients who held their breath in inspiration, and we also tried to carry out the procedure in as short a period as possible. We believe that by application of such a technique the danger of rupturing the spleen and of reflux through the puncture canal is less. The same conclusion was reached by MILNES WALKER et al.

In contradistinction to KONOR and SEN GUPTA, we consider that it is necessary to check the iodine sensitivity before performing the examination. We are satisfied with the intravenous test, which is generally accepted as the most reliable one; we see no reason for applying four different tests in every case, as is the practice of BOULVIN et al.

While COOPER et al., KONOR and SEN GUPTA, MILNES WALKER et al., DREYER and BUDTZ-OLSEN, and of late, LEGER et al., perform the puncture under local anaesthesia, BAHNSON et al. and DE SCOVILLE and LEROUX sometimes employ general anaesthesia while BOULVIN et al.

do not consider either as necessary. In our experience, the local application of an anaesthetic is necessary, for in this way any sudden movement of the patient during the puncture will be avoided, while the danger of damaging the capsule will be diminished. This is the more necessary since we make a skin incision at the site of the puncture, enabling us to introduce the point of the lumbar puncture needle without having to exercise excessive pressure. There is thus less danger of the needle penetrating too deep into the spleen after overcoming the initial resistance. The injection itself of the contrast medium is, according to the patients, always painless.

The amount of contrast medium recommended by the individual authors varies between 12 and 40 ml, the average amount being 20 ml and, in our experience, this amount will suffice provided that the conditions of the technique are satisfactory. It seems that MILNES WALKER et al. are the only authors to use 30 ml of contrast medium as a routine measure. Most authors work with 70 % concentrations of the contrast medium, while FULD and IRWIN have performed almost all of their examinations with 50 % solutions.

All authors agree that the injection speed should be as high as possible, but that the injection pressure should not be exaggerated. In agreement with SOTGIU et al., we feel that the application of an apparatus for the automatic injection of the contrast medium in PLPV is not advisable; it is necessary that the pressure should be regulated in accordance with the resistance offered by the parenchyma of the spleen in each individual case, which is only possible when the injection is performed by hand.

We see no justification for employing adrenalin in individual cases (BOULVIN et al., DE SCOVILLE and LEROUX) for the purpose of the better visualization of the lieno-portal circulation; the puncture in itself produces contraction of the spleen, as we could establish in a number of cases. SOTGIU et al. are also against the exhibition of adrenalin in PLPV. They hold that the injection of the contrast medium produces contraction of the spleen. COOPER et al., however, observed at operation contraction of the spleen at the moment of puncture even without any contrast medium being injected.

We applied the technique of serial roentgenography in our first PLPVs performed in March 1952, independently of BAHNSON et al., ABEATICI and CAMPI, and LEGER et al. Rapid serial roentgenography recently employed by us has further strengthened our conviction concerning the indispensability of this technique. Even to-day, most authors expose only 2 to 3 films at 2 to 5 second intervals. BOULVIN et al. control the injection by means of a diascope and then pass over to serial roentgenography. In our opinion this technique offers no advantages.

By means of rapid serial films we were able to establish that 0.5 sec. after the commencement of the injection, 5 to 7 cm of the v. lienalis was filled. This corroborates our previous presumption that contraction of the spleen does not participate actively in expelling the contrast, particularly as at the moment of injection the spleen is already contracted. LEGER et al., DE SCOVILLE and LEROUX, BOULVIN et al., and KONOR and SEN GUPTA consider the contraction of the spleen an important factor in the transportation of the medium injected. LEGER even assumes that a slow excretion of the contrast medium in individual cases is caused by a lessened capability of the spleen to contract. It would seem more probable that the injection speed, the amount of contrast medium, the pressure under which it is injected, as well as vascularization of the spleen, are the dominant factors. The matter undoubtedly demands further study by means of special rapid serial roentgenography.

The question of complications likely to occur in PLPV is still insufficiently dealt with. We have, for instance, found only scanty data on the number of cases in which a more pronounced reflux through the puncture canal occurred. This in spite of the fact that among the films found in the publications of LEGER et al., BOULVIN et al., and BAHNSON et al., typical cases of the contrast medium entering the abdominal cavity, may be encountered. Individual authors (BAHNSON et al., LEGER et al., KONOR and SEN GUPTA) are of the opinion that in these cases the contrast medium collects sub-capsularly, whereas it seems more likely that a collection occurs in the capillary space between the surface of the spleen and the surrounding organs. Pain in connection with PLPV is described variously by different authors. KONOR and SEN GUPTA, state that pain in the region of the spleen persists for 10 minutes after the injection and assume that it is possibly a consequence of splenic contraction. COOPER et al., further state that one half of their patients experienced pain in the upper left quadrant of the abdomen; it was of varying intensity and lasted from a few hours to several days. Data on para-lienal injection of the contrast medium are likewise scanty. Once BAHNSON et al. injected the whole amount of the contrast medium outside the spleen and into the abdomen, MILNES WALKER et al. made the injection into the gastroepiploic omentum, while FULD and IRWIN state: "Several times we failed to hit the spleen and diodone was injected into the peritoneal cavity, and on at least one occasion, into the splenic flexure of the colon." LEGER et al., KONOR and SEN GUPTA, and other authors, never mention this kind of complication, but are content to state that an intra-peritoneal injection of the contrast medium carries with it no untoward effects. In spite of the experimental investigations performed to this day emphasizing the harmlessness of an intraperitoneal injection of a 70 % contrast medium into the abdomen, it

is our opinion that we should continue with the study of this problem, and at the same time, pay greater attention to the examination of the spleen and its surroundings in splenectomies carried out subsequent to PLPV. The painful sensation in the upper left quadrant of the abdomen after PLPV is most probably a consequence of peritoneal irritation, and it is hard to believe that this can persist without any ill-effects.

Only of late has greater attention been paid to the complication we fear most when puncturing the spleen, *i. e.* bleeding. Thus, for instance, LEGER et al., who, in their first papers, are of the opinion that after the puncture no bleeding occurs, state in their latest paper that at operation performed immediately after PLPV they found several ml of free blood or coagulums in the abdominal cavity, although most frequently only ecchymoses under the capsule of the spleen. BAHNSON et al. state that in 3 cases operated upon immediately after puncture they found 30 to 40 ml of blood in the abdomen; COOPER et al. found not more than 50 ml of blood in the abdomen in any of the 4 operated cases; DE SCOVILLE and LEROUX, in one case of laparotomy performed 15 days after PLPV, found a little blood; and KONOR and SEN GUPTA, in two cases of cirrhosis, drew off some of the ascitic fluid before and after PLPV, finding some blood at the second puncture. In all our patients operated on shortly after PLPV, we found 30 to 60 ml of blood in the abdomen. COOPER et al., who in one case punctured a normal spleen without injecting contrast medium during laparotomy, were able to observe about 100 ml of blood flowing out after the withdrawal of the needle, after which the bleeding ceased spontaneously. The same authors state that in one of their cases shock supervened several hours after PLPV in a patient with cirrhosis and ascites, accompanied by pain in the upper left quadrant of the abdomen. The disturbances disappeared following a 1,000 ml blood transfusion. The only case of splenectomy made necessary by PLPV was described by MILNES WALKER et al. They had punctured a normal spleen with a thick needle during a laparotomy for gallstones, the respiratory cycles being maintained during the puncture. There was no bleeding immediately after the puncture, but three days later signs of intraperitoneal haemorrhage appeared. The spleen removed displayed a broad rupture of the capsule and the authors are of the opinion that this was a case of intra-lienal haematoma which had perforated into the abdomen. From our experience, as well as on the basis of the data mentioned, we hold that even the standard technique may be accompanied by complications and that minor bleeding into the abdomen is a regular feature in PLPV, although clinically usually not manifest.

Histologic examinations (ABEATICI and CAMPI, LEGER et al., CACCIARI et al.) have not, up to the present, yielded — apart from minor haema-

tomas and infarcts of the spleen — definite evidence of lesions of the splenic parenchyma due to injection of a 70 % contrast medium.

So far, no case of thrombosis of the vv. lienalis and portae subsequent to PLPV has been described although, theoretically, one should reckon with such a complication. In this respect CHILD's data are most valuable. He performed 100 portographies at operation in animals, and 85 in man, by the injection of Diodrast 35 % and 70 % directly into one branch of the v. mesenterica superior without any untoward effect.

Unlike our first 14 cases, we found in individual cases of the second series the 'filling defect' described by DREYER and BUDTZ-OLSEN, as a consequence of non-contrast blood entering the v. portae from the v. mesenterica superior. However, in none of our cases did we establish such a dilution of the contrast medium as represented by DREYER and BUDTZ-OLSEN in Fig. 1 of their paper, and we hold that in this case the film was exposed prematurely. In our individual cases we could only observe a margin defect, measuring 1 to 2 cm, of the lower contour of the v. portae.

The interpretation of the findings in cases of occlusion of the vv. lienalis and portae represents no problem radiologically. Interestingly enough, visualization of the collateral circulation in thrombosis of the v. portae depends to a certain extent on the site at which the medium is injected. As evident from Fig. 13 a, the first injection, made into the caudal and lateral portions of the spleen, caused filling of the intercostal and abdominal veins, while at the examination carried out 5 days later, the contrast injected more medially and cranially emptied through the vv. gastricae breves into the veins of the cardia and oesophagus (Fig. 13 b). We should therefore not expect, in every case of thrombosis, to be successful in visualizing all the collaterals by means of PLPV.

The opinions of authors regarding PLPV findings in portal hypertension of intrahepatic genesis are varied. LEGER et al. are of the opinion that in cirrhosis the branches of the v. portae in the liver are narrowed, the ramification is effected at an acute angle, and the branches are straightened out and rigid. SOTGIU et al. describe a widening of the v. portae, weakly expressed branches of the first order, and the non-existence of small branches. In their opinion, the angle between the v. lienalis and v. portae in cirrhosis becomes obtuse owing to the v. portae passing in lateral and cranial directions in conjunction with a shrivelling of the liver parenchyma. KONOR and SEN GUPTA state that in cirrhosis the intra-lienal branches are visible but poorly or not at all, and that the extra-lienal part of the v. portae is widened and tortuous. BOULVIN et al. describe in cirrhosis scanty rigid branches of the v. portae. LE GO is of the opinion, that in cirrhosis verticalization of the v. portae occurs, and he recommends measuring the angle between the v. portae

and vertebral column. CACCIARI and FRASSINATI describe the progressive narrowing of the lumina of the vv. lienalis and portae, along with a strengthening of the collateral circulation, in a patient with cirrhosis on whom they performed PLPV three times within a period of 9 months. STEINBACH et al., who performed transparietal portal venography by direct puncture of the v. portae, find in cirrhosis thin and scanty branches of the v. portae which end in a rich plexus composed of tiny and diffusely distributed blood vessels.

From our experience, we separate the signs of portal hypertension into certain and probable ones. The first group embraces a strong reflux into the tributaries of the lieno-portal venous system, development of the collateral circulation through the pre-existing anastomoses — including widened para-umbilical veins, and a marked slowing down of the circulation in the liver. According to our classification, the group of the probable signs embraces widening of the vv. lienalis and portae, and markedly tortuous course of these veins. These signs by themselves are insufficient for a diagnosis of portal hypertension, but only if combined with the individual signs of the first group. We are very sceptical in regard to the so-called typical appearances of ramifications of the v. portae in the liver in cirrhosis. In our 12 cases of cirrhosis we succeeded 8 times in visualizing the portal branches well and these did not show essential changes (Fig. 11 a—b). In our opinion, it is just the slowing down of the circulation in the liver — shown by rapid serial roentgenography — that enabled us to obtain in cirrhosis such a good visualization of the branches. The scantiness of the branches in the liver described by other authors as characteristic of cirrhosis of the liver is the result of films prematurely obtained in a slowed-down circulation in the liver. This is quite understandable if we consider that in cirrhosis the time of circulation is almost doubled, so that if only 2 to 3 films are taken at the usual time intervals, the contrast medium will not reach the branches of the v. portae during the examination. This is corroborated by one of our cases (Fig. 10), in which, on the basis of PLPV, we considered that we were concerned with a block in the region of the porta hepatis itself, whereas the post-mortem showed that the v. portae was normally patent. An analogy is to be found in the latest paper of LEGER et al. under the diagnosis of lienal bilharziosis, in which no intrahepatic branches of the v. portae were visualized, while the post-mortem finding was normal. We are of the opinion that in both cases the last film was made too early. The only change which we were able to establish in the branches of the v. portae in individual cases of severe atrophic cirrhosis was that they are shorter and less distant from each other than usual, which is understandable in view of the basic pathologic process of the parenchyma. Measurements of the angle between

the v. lienalis and v. portae (SOTGIU et al.), or between the v. portae and vertebral column (LE GO) in our material, did not yield any practical results in cirrhosis.

The application of rapid serial roentgenography will make the utilization of PLPV of even greater advantage for diagnosing intra-hepatic expansive growths (metastases, primary tumours, cysts) and vascular malformations, as well as for a more exact study of the speed of the circulation in various diseases. In our material, we had no opportunity to apply PLPV in metastases of the liver (LEGER et al., PEDRO PONS et al.), metastases in the porta hepatis (FULD and IRWIN), tumours of the pancreas (COOPER et al.), growths of the stomach (DE SCOVILLE and LEROUX), nor in the control of porto-caval anastomoses (MILNES WALKER et al., COOPER et al.). Puncture of the normal spleen is much more difficult and often ends in failure (FULD and IRWIN), in spite of the technical modifications recommended (COOPER et al., FULD and IRWIN), so that we have not used it so far.

Conclusions

Percutaneous lieno-portal venography (PLPV) is a reliable diagnostic method, easy to perform, but not without danger. It should, therefore, be employed only if blood transfusions and surgery are available.

This method enables us to follow the course, size, and the position of the v. lienalis and v. portae. It is possible by using it to correct a clinically postulated erroneous diagnosis of lieno-portal thrombosis. On the other hand, in the case of an existing thrombosis of the v. lienalis or v. portae, or both, the method has the advantage of showing exactly the situation of the thrombosis and revealing the collateral circulation. The procedure also is an important adjunct in diagnosing anomalies in the lieno-portal venous system. It enables the surgeon to differentiate preoperatively an extrahepatic obstruction from an intrahepatic one.

Serial roentgenography presents an opportunity of studying the circulation time of the lieno-portal system; it is particularly important in avoiding errors in the interpretation of the appearances.

SUMMARY

The communication forms an amplification of the one presented by the authors eighteen months ago, and is based upon 61 cases in 7 of which rapid serial roentgenography with automatic movement of the film was employed. The opinion is expressed that the procedure is indicated in every case of portal hypertension of unknown origin and presents a unique opportunity of localizing an obstruction and detecting anomalies in the lieno-portal circulation pre-operatively.

ZUSAMMENFASSUNG

Die Mitteilung bildet eine Erweiterung der von den Verfassern vor 18 Monaten gemachten Veröffentlichung und gründet sich auf 61 Fälle. Bei 7 Untersuchungen wurden schnelle Serienröntgenaufnahmen bei automatischer Bewegung des Filmes benutzt. Es wird der Meinung Ausdruck gegeben, dass diese Prozedur in jedem Falle mit Portahypertension unbekannter Ursache indiziert ist und dass sie eine einzigartige Gelegenheit darbietet, präoperativ einen Verschluss zu lokalisieren und Anomalien der lieno-portalen Zirkulation zu entdecken.

RÉSUMÉ

Cette communication constitue un développement de celle que les auteurs ont présentée il y a dix-huit mois et est basée sur 61 cas. Un sériographe rapide avec entraînement automatique du film fut employé en 7 cas où fut employé un sériographe rapide avec entraînement automatique du film. Les auteurs expriment l'opinion que cette technique est indiquée dans tous les cas d'hypertension portale d'origine inconnue et offre la seule possibilité de localiser une obstruction et de déceler les anomalies de la circulation spléno-portale avant l'opération.

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ROENTGEN DIAGNOSIS OF SMALL POLYPS IN THE COLON AND RECTUM

by

Lars Andrén, Sture Frieberg and *Sölve Welin*

"Polyp detection is cancer prevention" runs a slogan, launched a few years ago by the American Cancer Society. For American investigators seem to be fairly well agreed that there exists a very close connection between cancer and polyps — of which 70 % are adenomas — in the digestive tract; this is considered to be especially so in the case of the large bowel. It is believed that it has been possible not only to show a definite tendency for adenomas to become malignant but in many cases to demonstrate the direct development of a benign polyp to a malignant growth. It is also supposed that the majority of carcinomata of the colon arise from a polyp. The proof of the etiologic connection would appear to be, firstly, the repeated histologic findings of cancerous tissue within a limited area in an otherwise benignant polyp; secondly, the frequent development of carcinoma where previously a polypoid lesion had been diagnosed; thirdly, the frequency with which the presence of one or several polyps have been shown in the vicinity of an adenocarcinoma — this is especially true of multiple cancers; and finally, polyps and carcinomata reveal about the same rate of distribution in the different segments of the large bowel. Stress should perhaps be laid on the very pronounced tendency to malignancy in the familiar polyposis.

Should it be agreed that adenomata are potential carcinomata, then their detection and removal should constitute a prophylaxis against carcinoma in the large bowel. That this condition is relatively common is seen in statistics published in 1945 by the American Life Insurance Company. According to these figures, not less than 17 % of all deaths from cancer originate in malignant growths in the colon and rectum.

It has therefore become of urgent necessity to render still more effective the roentgenologic examination of the colon; for only rarely may small polyps be detected by the older technique, based on the ordinary barium

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sulphate enema. WEBER, who is one of the outstanding figures in this field, maintains that we must improve our diagnostic methods by all the means at our disposal so that we may eventually diagnose polyps, even only 5 to 10 mm in diameter. The method we have chosen to follow is based partly on that of FISCHER, the so-called double contrast method, partly on the mucosal pattern examination after the addition of 1 % tannic acid to the opaque enema, and partly on the use of the high voltage technique with a semi-transparent contrast medium, initiated by LEDOUX-LEBARD and GARCIA-CALDERON. In addition, efforts have been made to improve the contrast agent. Colloidal barium has been used in some quarters while in others, various substances, such as carboxymethylcellulose and dextran, have been added to the contrast medium. To judge by results, not one of these new contrast agents has hitherto brought about any remarkable improvement.

The first condition for more effective diagnostics of the colon — whatever method be chosen — is that the intestines must be as clean as possible. This is partly achieved by the use of evacuation agents, of which castor oil is still the most important, partly by a cleansing enema, and partly by diet. An ordinary water enema, however, is usually partially retained in the bowel. A colon contracting agent is therefore added. One of these is tannic acid, although 'Neodrast' or dioxyphenylisatin, which is closely related to the purgative Isacen, is far more effective. The latter produces especially vigorous contracting movements in the large bowel, and frequently such a complete evacuation of the contrast enema is obtained that none is visualized in the subsequent roentgenograms.

Another factor of importance is that the amount of mucus coating the colonic walls should be as small as possible; on the one hand, the mucus prevents adhesion of the contrast medium, and, on the other, small polyps may be obscured by its retention. Our patients are, therefore, always prepared with belladonna, which reduces the mucous secretion. According to WEBER, belladonna should, moreover, facilitate the patients' ability to retain the enema. Tannic acid also decreases mucous secretion and brings about an improved adhesion of the contrast medium. For this reason, we also add tannic acid to both the cleansing and contrast enemas and generally obtain a barium coating of the intestinal wall sufficient to demonstrate the mucosal pattern. It is also of great importance to keep the patient on a light diet the day before the examination. This greatly facilitates the clearing of the large bowel.

Technique

We prepare and examine our patients in the following manner.

1. The day preceding the examination, before noon, the patient is given an ounce (30 ml) of castor oil. He is kept on a light diet and a wash-

out is given in the evening. A similar wash-out is administered on the morning of the examination.

2. On arrival at the department, the patient at once receives 15 mg of Extractum belladonnae, followed by a second cleansing enema, to which is added 1 tube of Neodrast, containing 50 mg of dioxiphenylisatin, and tannic acid solution to constitute a 0.75 % solution. As the enema runs in, the patient is directed first to lie on the left side, and then on the right. He must then be given adequate time for the evacuation of the enema.

3. It may be said that we use a combination of the three previously mentioned methods of roentgen examination except that we employ a fairly dense contrast medium in place of a semi-transparent one. In order to achieve what in our experience is the most suitable contrast coating of the mucous membrane of the bowel, the solution is standardized at 6.5 by Philips' barium tester. Neodrast and tannic acid are added in the same proportions as in the previous wash-out.

The contrast enema is allowed to flow only as far as the middle of the transverse colon, when the usual postero-anterior, oblique and profile views of the rectum and sigmoid colon as well as the splenic flexure, are obtained. Should more of the large bowel be filled, there is risk of the material, on evacuation, forcing its way into the small bowel. Visualization of the sigmoid colon is then rendered difficult by super-imposition of contrast-filled coils of the ileum.

4. The patient is then directed to evacuate the enema, and it is decided by fluoroscopy whether the evacuation has been sufficient for the mucosal pattern relief film. If this is not the case, the patient is instructed to attempt to evacuate more of the bowel contents. In spite of the contrast enema being only allowed to reach the middle of the transverse colon, a thin coating of the greater part of the large bowel is usually obtained. In American quarters, it is claimed that lesions down to one centimetre in diameter may be diagnosed from such a mucosal pattern roentgenogram; this, however, would not appear to be always possible.

5. Before insufflation, more contrast medium is injected. The quantity required varies from case to case, but must be sufficient to ensure filling of the bowel as far as the middle of the sigmoid colon.

6. Air is now blown into the bowel by means of a clysto pump. The patient is rotated fully to the left, preferably several times, in order that air and contrast medium shall be equally distributed over the entire intestinal wall. After controlling by fluoroscopy that the caecum has been outlined, the patient should be fully rotated once or more to the right. The contents of the rectum are then drained off by means of an enema pipe with the patient in the prone position. This procedure may have to be repeated one or more times if too much material is left in the bowel.

Should too much air escape during these drainings, more must be pumped in so that the entire bowel becomes satisfactorily distended.

As rotation of the patient is, in our experience, a most satisfactory method of ensuring filling, the use of more complicated insufflation instruments such as 3-way taps and similar apparatus appears to be unnecessary.

7. Films are now taken of the colon in oblique projections in both the prone and supine positions; a profile view of the rectum and sigmoid colon may also be included. Views are then taken with a horizontal beam in both the standing and right and left recumbent positions. In both of the last-mentioned projections, care should be taken to see that the whole of the rectum is included. In order to achieve good quality roentgenograms in spite of the fact that the distended bowel often lies at a considerable distance from the film, a long focus—film distance is required. We ourselves use a distance of 1.5 metres. In addition, it is desirable to employ a roentgen tube of fine focus (1.2 mm in diameter). Since there are scarcely any movements in the distended bowel, we have found it more suitable to use a small focus and relatively long exposure than a larger focus and shorter exposure.

8. After all the required radiographs have been taken, the air is released with an enema tube, the patient being on his right side and in the prone position.

Material

1,274 patients have been examined with this procedure (1/12/1953—15/8/1954) which has now become a routine method. The patients are drawn from ordinary out- and in-patients; there is no question, therefore, of a specially selected material. Only patients who are very weak or seriously ill are examined with the older, simple contrast medium enema: it must be admitted that the accompanying pain caused by Neodrast and tannin, undoubtedly constitute a certain strain. In cases of suspected chronic appendicitis, the older method is also employed.

Results

Using the technique described, we have found one or more polyps in 159 patients in the period. It is, of course, true that cases that have not yet been surgically verified are also included in this figure, but the majority of these have been examined twice with similar results. Of the 159 positive cases, 81 were men and 78 women. Their ages are given in Table 1. As shown in the table, the low figures in the higher age-groups are due to the number of patients examined being considerably smaller. Since we have examined a total of 1,274 patients (624 male, 650 female) during the above-mentioned period, a positive result in 12.5 % has been obtained.

This is in good agreement with the frequency found in the section material (BUIE, STEVENSON).

Table 1

Age distribution of cases of polyps

	No. of cases of polyps	No. of cases examined	%
0–10 years	3	15	20
11–20 »	3	23	13
21–30 »	8	99	8
31–40 »	23	210	11
41–50 »	29	260	11
51–60 »	42	309	14
61–70 »	39	260	15
71–80 »	11	89	14
81–90 »	1	9	11
Total:	159	1,274	12.5 %

The situation of the polyps is shown in Table 2. In drawing up the latter, we have throughout placed distally polyps found at the junctions of the different intestinal segments. Details regarding positions are, nevertheless, only approximate on account of the considerable displacement of which polyps are capable.

Table 2

Frequency in different intestinal segments

	No. of cases	%
Rectum	99	46.4
Sigmoid colon	45	21.0
Descending colon	29	13.6
Transverse colon	29	13.6
Ascending colon and caecum	12	5.4

The table shows that we have diagnosed a remarkably high number of polyps in the rectum. This is due to the patients, before proctoscopy, generally being roentgenologically examined. Proctoscopy, during this period, has only in one case revealed polyps which had not been diagnosed at the previous roentgen examination. On the other hand, repeated proctoscopies have had to be carried out in order to demonstrate polyps already shown by roentgen examination. This would suggest that the roentgenologic investigation of the rectum can well hold its own with proctoscopy as far as the diagnosis of polyps are concerned.

The table further shows that in approximately half the cases the polyps were situated above the level of the proctoscope. In comparison, STEVENSON's figures may be quoted. He found polyps above the proctoscopic level in 1.9 % of 1,500 patients examined with the double-

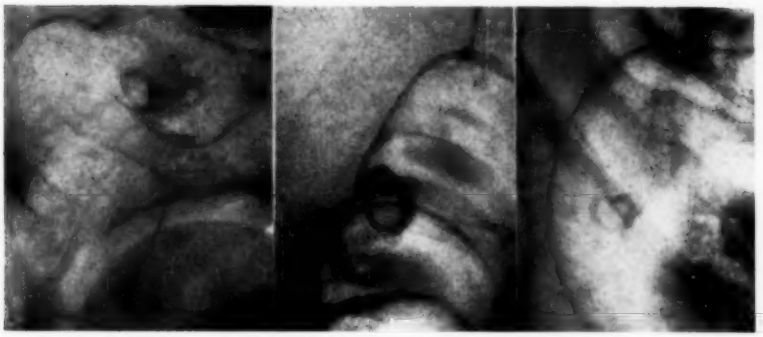

Fig. 1. Examples from cases of small polyps of the colon.

contrast technique. Five hundred of these had rectal bleeding or previously demonstrated polyps; polyps were found in 5 % of this group. Of the remaining 1,000 patients who had not had bleeding nor previously shown polyps, only 0.4 % were found to have polyps. Our corresponding figures for polyps above the proctoscopic level were about 12 % and 5.4 % respectively.

The sizes of the polyps are given in the table below.

Table 3

The sizes of the polyps measured in the radiographs

Size	No. of cases
0— 5 mm	131
5—10 »	60
10—15 »	12
15—20 »	4
20—25 »	4
25—30 »	1
over 30 »	2

The table shows that not less than 191 of the 214 (90 %) polyps demonstrated were less than 1 cm in diameter. It should also be noted that the mensuration was made in the radiograph without any reduction for the degree of enlargement. Furthermore, it should be pointed out that 131 (60 %) polyps were less than 5 mm in diameter, and some of those verified were as small as 1 to 2 mm (see Figs. 1 and 2). The increased frequency of polyps in our material in comparison with others may be ascribed to the fact that we largely succeeded in detecting the smaller polyps. This is in all probability a result of the tele-roentgenography combined with a fine focus, of the use of a dense contrast medium, and of the fact

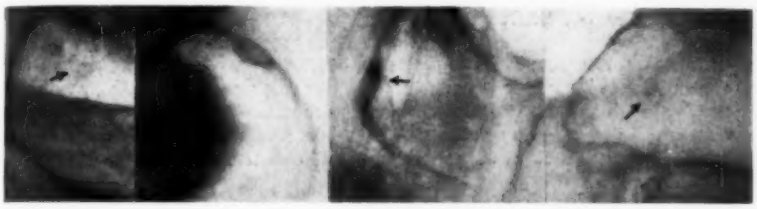

Fig. 2. Examples from cases of very small polyps of the colon.

that in so many cases we were able to achieve satisfactory clearing of the large bowel.

It is striking how small the pedicle appears in the greatly distended bowel. This would seem to be due probably to the pedicle on distention becoming part of the intestinal wall, thus ensuring a more exact localization of the polyps than in the mucosal pattern films or in the ordinary contrast enema.

Of the polyps demonstrated roentgenologically, 66 have been verified either by means of surgical intervention, laparotomy + colotomy (15 cases), or by proctoscopy + excision (51 cases). A number of cases of polyps from the autumn of 1953 — when the technique was still being worked out — are also included in these figures.

Of the polyps removed, 12 % (8 cases), were undoubtedly carcinomata. In this connection we wish to point out that these cases were not differentiated from the ordinary ones, clinically, macroscopically, nor roentgenologically; one of these polyps did not measure more than 2 × 2 mm in diameter. Furthermore, in the opinion of our pathologist, 30 % in all were clearly precancerous.

SUMMARY

A material of 1,274 cases was examined with the so-called double-contrast enema method and polyps were found in 12.5 %; of these, approximately 90 % were under 1 cm and 60 % under 0.5 cm in diameter. The result is ascribed to careful preparation, special techniques giving true double-contrast representation of the entire colon, tele-roentgenography, the use of fine focus tubes and a dense contrast medium.

ZUSAMMENFASSUNG

Ein Material von 1.274 Fällen ist mit der sog. Doppelkontrasteinlaufmethode untersucht worden. In 12.5 % der Fälle fand man Polypen; von diesen hatten ungefähr 90 % einen Durchmesser von weniger als 1 cm und 60 % von weniger als 0.5 cm. Die Ergebnisse werden mehreren Faktoren zugeschrieben, nämlich sorgfältiger Vorbereitung, spezieller Technik zur Erzeugung wirklicher Doppelkontrastdarstellung des ganzen Colon, der Teleröntgenographie, der Benutzung von Feinfokusröhren und einem dichten Kontrastmittel.

RÉSUMÉ

Les auteurs ont examiné 1,274 cas par la méthode du lavement baryté dit en double contraste et ont trouvé des polypes dans 12.5 % des cas; de ceux-ci, 90 % avaient moins de 1 cm et 60 % moins de 0.5 cm de diamètre. Ces résultats sont attribués à une préparation soigneuse, à des techniques spéciales donnant une image en véritable double contraste du colon en son entier, à la téléradiographie, à l'emploi de tubes à foyer fin et à un produit de contraste dense.

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ROENTGENOLOGIC DIAGNOSIS OF BRONCHIECTASIS

An analysis of 112 Cases

by

Carl E. Gudbjerg

Bronchography occupies a central position in the selective method of segmental resection of bronchiectatic lung tissue in modern thoracic surgery.

In large radiologic departments where bronchography is a daily occurrence, this method of examination is regarded as an easy and simple procedure, whereas this cannot be said to be the case in smaller clinics in which bronchography does not form part of the daily routine.

It is therefore of great value to be able to elicit the greatest possible amount of information from the routine chest roentgenogram. In correlating this with the clinical manifestations, it will in the majority of cases be possible to form a well-founded opinion as to the presence or absence of bronchiectasis. It is especially on this point that the conventional roentgen examination of the lungs is of importance, and even though the chest roentgenogram does not reveal changes which are specific or pathognomonic of bronchiectasis, this examination is a far more valuable diagnostic aid than is generally assumed. However, for the establishment of an unquestionable diagnosis and as a preoperative guidance for the surgeon, bronchography will always be necessary.

As in all other problems related to bronchiectasis, considerable difference of opinion exists as to the diagnostic value of the routine roentgenogram.

FISCHER (1952) states that the chest roentgenogram is rather uncharacteristic, and in SCHINZ' textbook only brief mention is made of the changes which may be demonstrated. He emphasizes that the diagnosis can be made only by bronchography.

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TESCHENDORF (1939) is of the same opinion, and CAFFEY, in his textbook of 1950, states that visible changes are present only in advanced cases, and that even the chest roentgenogram may be perfectly normal.

On the other hand, RUBIN (1947) attaches greater importance to the routine roentgenogram. He says that even though, at first glance, the appearance of the film may seem non-informative, it is unusual to find a patient with established bronchiectasis in whom the roentgen findings are strictly within normal limits. RUBIN bases his statements mainly on the investigations of ANDRUS (1940), who, after a detailed study of the radiographic features of bronchiectasis, emphasized its four 'cardinal signs', viz., 1. Generalized increase in density of the pulmonary markings; 2. Ring shadows; 3. Displacement of the heart and diaphragm; 4. Chronic pneumonia.

In the opinion of ANDRUS, the presence of any one of these warrants the suggestion of bronchiectasis. If two of these 'cardinal signs' are well established, the suggestion is greatly enhanced, and the diagnosis is practically certain in the presence of three or more of these changes, although any certainty depends on the degree of the changes and on associated clinical signs. Admittedly, it appears from ANDRUS's paper that the term 'chronic pneumonia' refers to roentgenographic changes in the chest film, but nevertheless it must be considered illogical to use this term, which might just as well cover a clinical condition, in conjunction with such distinctly descriptive roentgenologic terms as the first three. It would, therefore, have seemed more rational to use, for example, chronic 'infiltration' instead of chronic 'pneumonia'.

LORENZ (1951) voiced a different opinion, stating that even advanced bronchiectasis often gives a negative chest roentgenogram. He writes: "Whereas routine chest roentgenograms are often diagnostic of tuberculosis, they may be of little aid in bronchiectasis." DIAMOND and VAN LOON (1942), in their series of 150 children, of whom one half had proved bronchiectasis, whereas the remaining half showed normal bronchographic appearances but similar clinical signs as the patients with dilated bronchi, found no conspicuous differences in the chest roentgenograms in the two groups. GOOD (1945) claimed that from the study of conventional chest roentgenogram the diagnosis may be suspected in about 75 % of all patients with bronchiectasis. LISA and ROSENBLATT (1943), emphasized particularly the importance of oblique and lateral views, especially if triangular atelectases are suspected. It seems unnecessary to emphasize this. On the slightest suspicion of the presence of a pathologic condition, films should obviously always be taken in several projections.

WARNER and GRAHAM (1933) were the first to describe this change in detail. In 6 % of their cases of bronchiectasis confirmed by broncho-

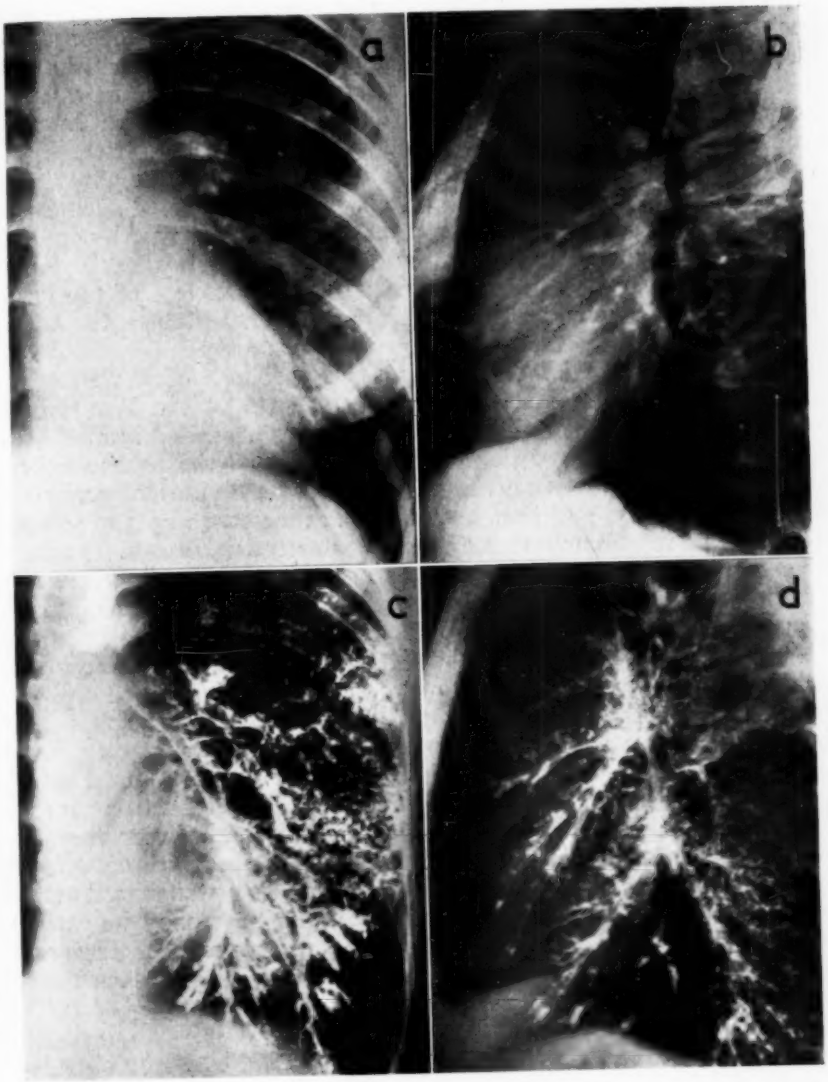

Fig. 1. Woman (14497/53), aged 24. a—b. Ordinary chest roentgenograms show normal conditions. c—d. Bronchography: Cylindrical bronchiectases in the lingula and the anterior basal segments of the left lower lobe. Confirmed by operation.

graphy, they found a triangular homogeneous area of increased density. One side of the triangle runs along the mediastinum, the lower side lies parallel to the diaphragm, and the hypotenuse extends from the hilum obliquely downwards to the lateral part of the lower side at a varying distance from the midline. On the left side, the triangular density is situated behind the heart, which is displaced to the left. If the density is on the right side, the mediastinum is displaced to the right, and the dome of the diaphragm is usually elevated on the affected side. Macroscopic and microscopic examination of specimens removed by operation revealed that the change was simply due to atelectasis which had developed on account of occlusion by inflammatory exudate of the lumina of the terminal bronchioles. In experimental studies in dogs, the authors were able to produce exactly the same appearances.

Fundamental studies on more massive collapse of the lung were carried out by JACOBÆUS and WESTERMARK (1930) and WESTERMARK (1935, 1938). In several cases, these authors demonstrated bronchiectasis in atelectatic segments of the lung; they explained the pathogenesis by assuming that obstructive atelectasis results in a diminished pressure in the thoracic cavity, and that a simultaneous increase in pressure within the lumen of the bronchus, due to marked secretion, occurs. The difference in pressure may be considerable and will then tend to dilate the bronchial wall, particularly in cases in which the tonus has become impaired as a result of previous inflammatory changes.

While it is generally agreed that bronchiectasis may be demonstrated with certainty only by bronchography, there is thus a marked difference of opinion as to the diagnostic value of the chest roentgenogram. However, even though it is possible only in rare cases directly to discern bronchial dilatations without instillation of a contrast medium, I believe, after having subjected 112 cases of proved bronchiectasis to a thorough analysis, to be able to demonstrate that, due to the inflammatory reaction in the pulmonary tissue, the disease is associated with certain phenomena. These are relatively characteristic and so pronounced that in most cases a well-founded suspicion of the diagnosis may be gathered from the study of the ordinary chest roentgenogram; bronchography will, however, still be necessary for patients in whom surgical treatment is contemplated.

Personal investigations

An analysis of the changes observed in the chest roentgenograms and bronchograms of 112 patients with bronchiectasis is given below. In addition, in the patients subjected to operation the specimens removed were studied both macroscopically and microscopically, and the changes disclosed were then compared with the roentgen evidence.

The case material studied originated mainly from the Department of Thoracic Surgery of the University Hospital, Copenhagen, and consisted of 112 patients, of whom 54 were men and 58 women, the average ages of the men and women being 39 and 36 years, respectively. Of the patients, 66 were subjected to operation, viz. 23 men and 43 women, their average ages being 38 and 31 years, respectively. One patient was treated with thoracoplasty and two with segmental resection, while 57 were subjected to lobectomy and six to pneumonectomy. The sex and age distribution of the patients appears from Tables 1 and 2.

Table 1

Sex and age distribution in 112 patients with bronchiectasis

Age, in years	Under 11	11—20	21—30	31—40	41—50	Over 50	Total
Males	3	2	4	17	13	15	54
Females	0	11	17	13	7	10	58
Total	3	13	21	30	20	25	112

Table 2

Sex and age distribution in 66 patients operated for bronchiectasis

Age, in years	Under 11	11—20	21—30	31—40	41—50	51—60	Over 60	Total
Males	2	2	2	6	5	5	1	23
Females	0	11	14	11	4	2	1	43
Total	2	13	16	17	9	7	2	66

A. Chest roentgenogram

Space does not permit a tabular survey of all the patients studied: the results are shown instead in smaller tables in which the changes are indicated by +++ (pronounced), ++ (distinct), + (slight), and 0 (normal conditions).

The changes demonstrated, which will be considered separately, were four in number: 1. Increased pulmonary markings; 2. Honeycomb-like structures; 3. Atelectasis; 4. Pleural changes.

1. Increased pulmonary markings. To decide with certainty if the pulmonary markings are normal, it is essential that the films are as perfect as is technically possible. It is a fact that the standards of the normal for the same roentgenogram show considerable variation from department to department. Only by virtue of experience and practice in the interpretation of films extending over many years is it possible to assess if the pulmonary markings are within the limits of the normal or otherwise.

Table 3

Changes in the chest roentgenogram in 112 patients with verified bronchiectasis

Degree of changes	Increased pulmonary markings	Honeycomb-like shadows	Atelectasis	Pleural changes	Normal chest roentgenogram
+++	64 (57 %)	14 (13 %)	17 (15 %)	13 (12 %)	
++	24 (22 %)	12 (11 %)	10 (9 %)	25 (22 %)	
+	7 (6 %)	22 (19 %)	8 (7 %)	14 (13 %)	
0	17 (15 %)	64 (57 %)	77 (69 %)	60 (53 %)	8 (7,1 %)
Total	112	112	112	112	8

Greatly increased pulmonary markings were found in 88 (79 %) of the patients studied. In seven patients, less pronounced but yet definitely pathologic changes were observed. Only in 15 % of the patients were the pulmonary markings within normal limits.

The changes appeared in the films as accentuated densities, most frequently in the form of linear, relatively wide bands, which, unlike normal vascular markings, did not end in a tapered fashion towards the periphery. In most cases, these bands extended from the hilar regions down along the heart border. In the lateral view, they were often very distinct, usually extending from the hilar region downwards and backwards towards the posterior phrenico-costal sinus. The bands often crossed each other, thus forming a characteristic coarse-meshed network or more mottled patterns. The appearances, when pronounced, are rather characteristic, although not pathognomonic of bronchiectasis. Purely vascular conditions may result in similar changes, and there is not the least doubt that the increased density of the coarse-meshed pulmonary markings arouses suspicion of bronchiectasis in a larger number of cases than can afterwards be confirmed by bronchography.

The pathologic basis of the roentgenologic changes is scarcely the bronchitic condition as such. Thus, while increased density of the pulmonary markings may be observed in bronchiectasis in 85 % of the cases, it is a far less frequent finding in patients suffering from chronic bronchitis unassociated with bronchial dilatation. It is therefore not likely that, for example, oedema of the mucous membrane can be responsible for the increased pulmonary markings. Accumulation of secretions is unquestionably a contributory factor, but it is reasonable to assume that the increased shadows must, above all, be assigned to fibrotic changes in the peribronchial tissue. In practically all the patients, histologic examinations revealed pronounced unspecific, chronic inflammatory changes with a massive infiltration of lymphocytes and plasma cells, and peribronchial fibrosis often extending into the interstitial tissue. A more fibrosis-like pattern was occasionally seen in the basal

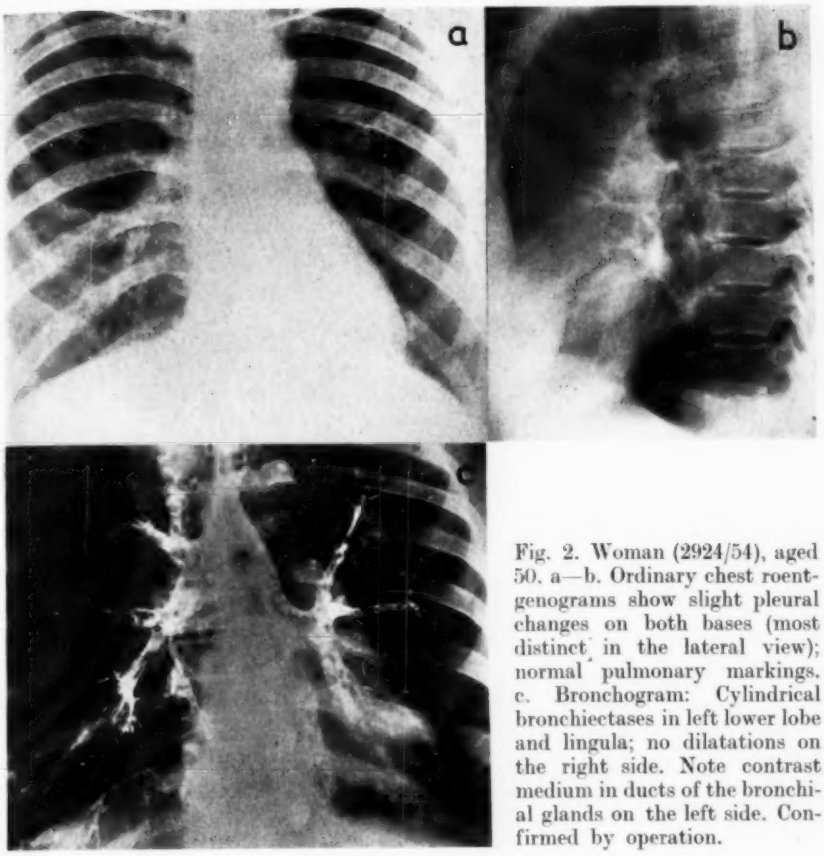

Fig. 2. Woman (2924/54), aged 50. a—b. Ordinary chest roentgenograms show slight pleural changes on both bases (most distinct in the lateral view); normal pulmonary markings. c. Bronchogram: Cylindrical bronchiectases in left lower lobe and lingula; no dilatations on the right side. Note contrast medium in ducts of the bronchial glands on the left side. Confirmed by operation.

parts of the lung fields. These appearances might be due to slowly healing or recurring bronchopneumonia, although it is, perhaps, more likely that it was a manifestation of small atelectases rather than of actual fibrosis. At all events, this observation must arouse a strong suggestion of the presence of bronchiectasis.

2. Honeycomb-like structures. Honeycomb-like structures are not quite as frequent. In the series studied, this change was observed in 43 % of the patients, although it was very distinct only in 24 %. On the other hand, when marked, the appearances are characteristic. They resemble those of congenital cystic degeneration, which is referred to as 'honeycomb lung'. In the typical picture, these formations appear as areas of

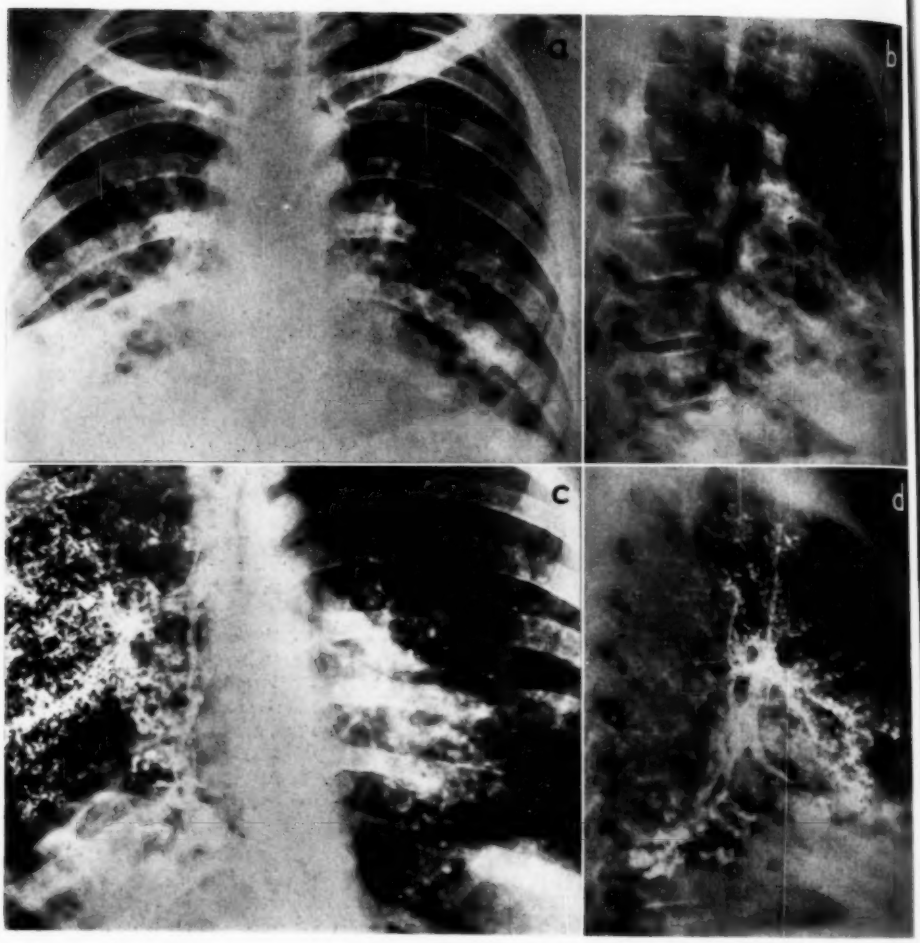

Fig. 3. Woman (2537/49), aged 38. a—b. Increased pulmonary markings, honeycombing basally (+++), and partially atelectatic right middle lobe. c—d. Bronchogram: Saccular and cylindrical bronchiectases in right middle and lower lobes and lingula. Confirmed by operation.

lessened density, ovoid or annular in shape, but more frequently showing more polygonal borders. The rarefied areas are surrounded by dense fibrotic bands, which together form a more or less extensive network.

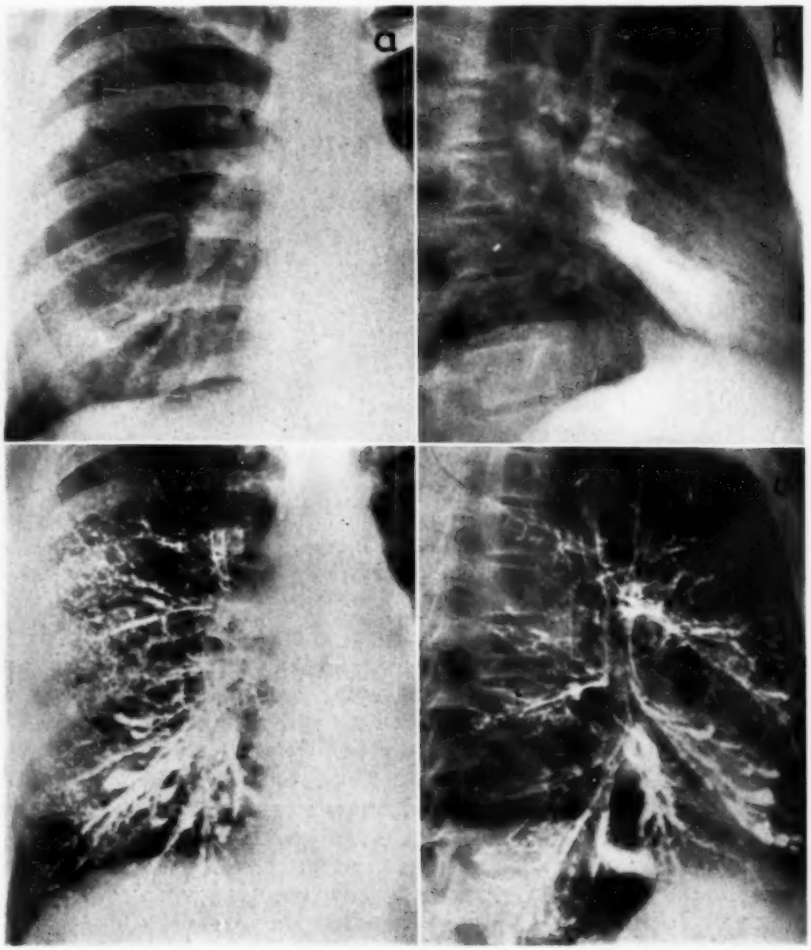

Fig. 4. Girl (16819/53), aged 15. a—b. Ordinary chest roentgenograms show sequelae of left-sided thoracotomy, performed two years previously, when the left lower lobe and the lingula were removed for cylindrical bronchiectasis. The right side reveals slightly increased pulmonary markings (+), slight pleural changes and a partially atelectatic middle lobe. c—d. Bronchograms: Cylindric and saccular bronchiectases in right middle lobe and anterior segment of right lower lobe. Confirmed by operation.

While fluid in the cavities is not an uncommon occurrence in the honeycomb lung proper, this phenomenon was not observed in the rarefactions described; nor did bronchography result in contrast filling

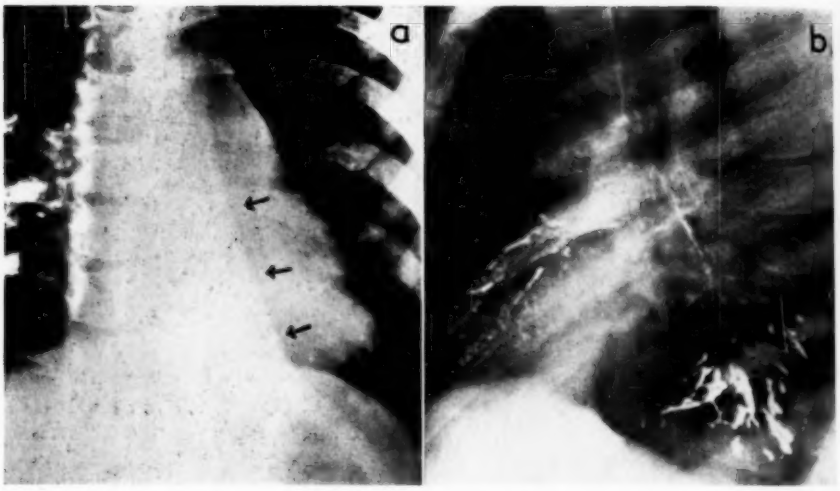

Fig. 5. Boy (13979/47), aged 10. a. Antero-posterior view. Triangular atelectasis of left lower lobe (visible through the heart), otherwise normal pulmonary markings. b. Bronchogram: Cylindric bronchiectases in left lower lobe. Confirmed by operation.

of the cyst-like cavities. The explanation is that the rarefactions in the roentgenograms do not actually represent dilated bronchi; the polygonal structures are due to accompanying emphysematous blebs surrounded by peribronchial fibrosis. This was confirmed by histologic examinations which in addition to fibrosis showed pronounced local emphysema alternating with fibrotic and atelectatic areas in the lung tissue.

Ordinary bullous emphysema and, in particular, congenital cysts may cause difficulties in the differential diagnosis. In the latter condition, however, the almost circular cavities are more sharply defined with less fibrosis and infiltration between the cavities. Congenital cysts which have never been infected may not produce any clinical signs, and the absence of such manifestations is therefore a further aid in differentiating congenital cysts from acquired bronchiectasis (LICHT 1942).

3. Atelectasis. The demonstration of total or partial lobar atelectasis should always arouse a strong suspicion of the presence of bronchiectasis, especially in children. Owing to the anatomic relationship, compression from surrounding lymph nodes may especially involve the right middle lobe in which but moderate enlargement of the nodes may give rise to bronchial occlusion. The so-called 'middle-lobe syndrome' occurs in this way; owing to impaired bronchial drainage, swelling and more or less pronounced atelectasis develops in the middle lobe, which

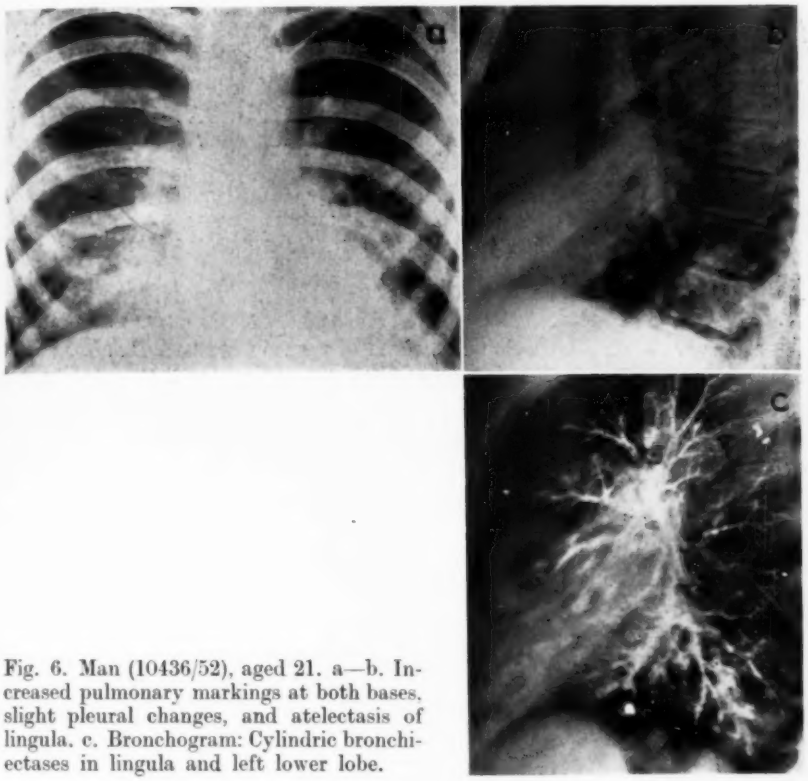

Fig. 6. Man (10436/52), aged 21. a—b. Increased pulmonary markings at both bases, slight pleural changes, and atelectasis of lingula. c. Bronchogram: Cylindric bronchiectases in lingula and left lower lobe.

in the roentgenogram appears to be consolidated, and after the resolution of the acute process its bronchial ramifications are often dilated.

Even massive atelectasis is, however, usually not due to occlusion of major bronchial branches. Both bronchography and the examination of specimens removed by operation show that the most important pathologic changes are localized to the bronchioles in which accumulation of inflammatory exudate with ensuing obstruction and atelectasis occurs. The alveolar filling of atelectatic segments is a rare occurrence in bronchography. The absence of alveolar filling is most frequently due to obstruction by accumulated secretions, but it can scarcely be doubted that in a considerable number of cases it must be taken as evidence of the absence of alveoli or a reduction in their number owing to destruction and replacement by fibrotic tissue. In the series studied, atelectasis associated with more or less pronounced displacement of organs was present in 35 patients

(31 %). Atelectasis was the only pulmonary change observed in six patients, of whom three were under 10 years of age. The sites of involvement were as follows:

Right middle and lower lobes	3	cases
Right middle lobe	14	»
Right lower lobe	6	»
Entire left lung	2	»
Left lower lobe	8	»
Lingula	2	»
	35	cases.

The triangular atelectasis described by WARNER and GRAHAM was observed in 7 % of all established cases of bronchiectasis. In all the cases in which atelectasis was demonstrated in the chest roentgenogram, this finding was fully confirmed by subsequent examination of the specimens removed by operation. In addition, small atelectatic areas with partially collapsed alveoli containing secretion or blood, which had not been demonstrated by the preceding roentgen examination, were often revealed by the histologic examination. If atelectasis without any other definite cause is demonstrated, a diagnosis of bronchiectasis should always be considered and the patient subjected to bronchography.

4. Pleural changes. Pleural thickenings and adhesions were found far more frequently at operation than it was possible to demonstrate roentgenographically. In the roentgenograms, 34 % of the patients showed distinct and 13 % slight changes, while practically all the patients subjected to operation had more or less pronounced adhesions.

The slight changes (+) indicated in Table 3 include flattening or obliteration of the phrenico-costal sinus, widened interlobar fissure, and small adhesions of the diaphragm. In the presence of further thickening along the thoracic wall or bilateral involvement, the cases were listed under ++, while pronounced changes (+++) include cases with considerable shrinkage and retraction. Evidence of tuberculosis was disclosed only in five cases, whereas tuberculous changes could not be demonstrated in the remaining patients; neither their past histories nor histologic examinations pointed in that direction. It must therefore be supposed that the pleural thickenings and, perhaps, particularly the diaphragmatic irregularities, had resulted from atelectasis in basal pneumonic processes rather than from tuberculous or any other forms of pleurisy.

Pleural changes were most frequently accompanied by other irregularities in the chest roentgenogram and were observed as an isolated phenomenon only in two patients. Pleural changes are of diagnostic value only when correlated with the severity of additional pulmonary changes

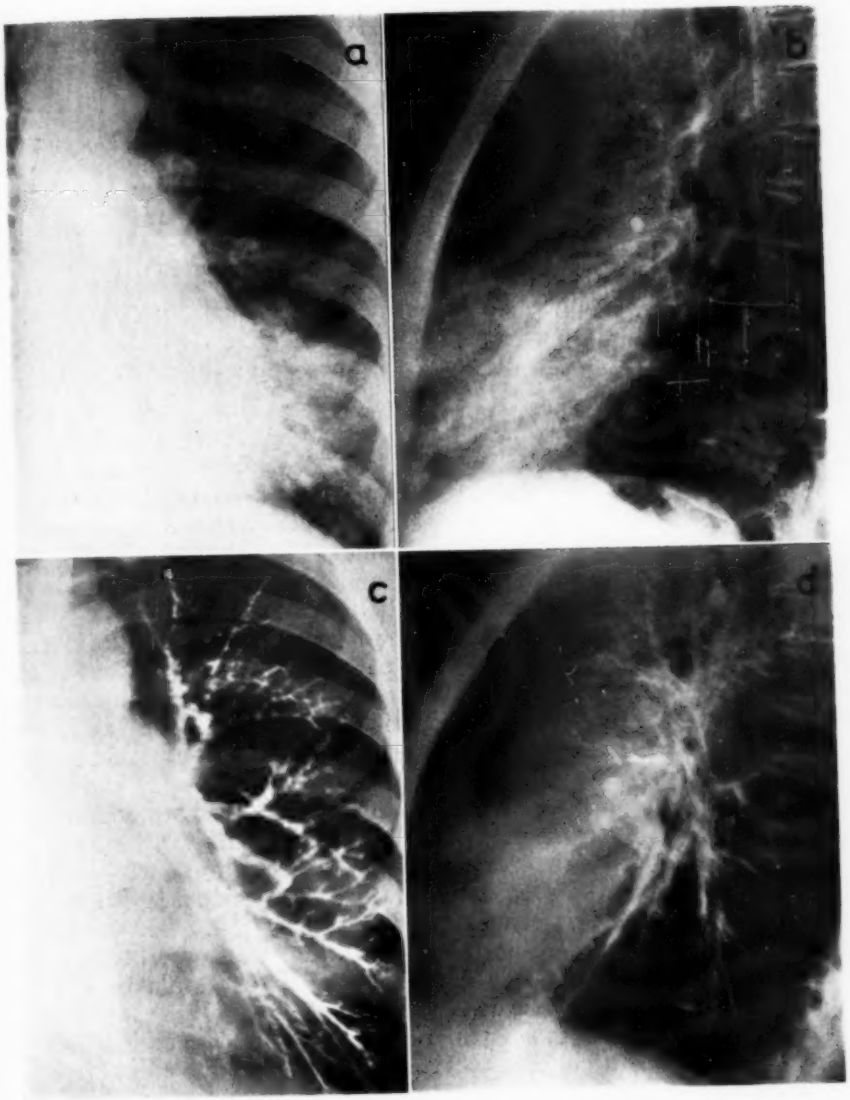

Fig. 7. Woman (287/53), aged 37. a—b. Ordinary chest roentgenograms. Infiltration at the left base, but otherwise normal conditions. c—d. Bronchograms: Cylindric bronchiectases in left lower lobe and lingula. Confirmed by operation.

and, in particular, clinical signs exhibited by the patient. Thus, even though pleural changes are not specific for bronchiectasis, their presence may nevertheless suggest that condition.

Conclusions. It appears that a perfectly normal chest roentgenogram is uncommon in bronchiectasis. Among 112 cases of verified bronchiectasis, this was found only in 7.1 % of the patients.

However, even though the chest roentgenogram does not reveal pathognomonic changes, its value is nevertheless so great that the experienced observer may with relative certainty arrive at the diagnosis. Increased density of the pulmonary markings, honeycomb-like structures and otherwise unexplained atelectases are of particular diagnostic value; recurring bronchopneumonias may also strongly suggest of bronchiectasis. On the other hand, no definite diagnostic value can be assigned to isolated minor pleural changes.

B. Bronchogram

The technique of bronchography will not be described in this paper. The transglottic route was used, with instillation of the contrast medium through a curved, blunt larynx needle under local anaesthesia. The contrast medium employed was iodized oil and, since January 1954, iodized oil to which sulphonamide was added (GUDBJERG 1954).

A bronchographic examination thoroughly performed gives information as to the type and extent of the pathologic process with great certainty. The problems of interpretation of the films are not quite as simple, however, as is generally believed. It may be extremely difficult to decide whether a segment of a bronchus is dilated or within normal limits. A criterion for dilatation usually employed is that the lumen remains unchanged in width and does not become narrow from the hilum towards the periphery. It is not a rare occurrence, however, to find segments in which the margins of the bronchus are somewhat irregular, so that it may be exceedingly difficult to decide whether ectasia is present or not. In this connexion it must be remembered that both postero-anterior and antero-posterior views are necessary, because the bronchus-film distance plays an important part in the evaluation of the calibre of the bronchus under consideration.

The classic division into cylindric, saccular, and combinations of these two types — according to the appearance of the dilatations in the bronchogram — is used below.

Further differentiation into tubular, fusiform, fusosaccular, ampullate, varicose, etc. has often been suggested. In my opinion, 'cylindric' and 'saccular' are fully adequate in describing the appearance of the dilatations, and the introduction of a complicated classification will only

create confusion and add to the difficulties of survey. Considering that the pathogenesis has no definite influence on the type, and that the clinical signs and the therapy are the same in all types, it is superfluous to introduce new descriptive terms. It must be emphasized that it is not possible beforehand, to guess as to the appearances in the bronchogram from the clinical manifestations; slight ectasia may very well give rise to pronounced clinical signs and, conversely, even well-developed bronchiectasis may be associated with relatively mild subjective reactions. In addition to dilatation, distinct contrast filling of the ducts of the bronchial glands was observed in six cases. This change, which appears as a cystlike projection from the bronchial wall, is, however, quite unspecific and only a manifestation of relatively severe inflammatory reactions in the mucous membrane (GUDBJERG and THOMSEN 1954).

GREENFIELD (1940) stated that in well-established bronchiectasis the calibre of the bronchi does not change upon inspiration and expiration due to destruction of the elastic elements of the bronchial wall, and hence concluded that well-established bronchiectasis is irreversible. This is well known, but even though I have not had an opportunity to study an extensive series of patients with this consideration in view, I believe

Table 4

Sites of involvement and type of dilatation in 112 cases of bronchiectasis

Segments involved	Type of dilatation			Total
	Cylindrical	Saccular	Cylindrical + saccular	
Entire right and left lungs	1	2	3	6
Right lung + left lower lobe	1	0	1	2
Right lung	1	0	2	3
Left lung + right lower and middle lobes	0	0	1	1
Left lung + right lower lobe	2	0	0	2
Left lung	2	1	4	7
Right upper lobe	3	1	0	4
Right middle lobe	6	1	1	8
Right lower lobe	5	0	2	7
Left upper lobe	1	3	0	4
Left lower lobe	9	3	6	18
Lingula	0	1	0	1
Right lower and middle lobes + left lower lobe	0	2	2	4
Right lower and middle lobes + lingula	0	1	1	2
Right lower and middle lobes	11	1	3	15
Right and left lower lobes + lingula	1	0	2	3
Right and left lower lobes	1	0	1	2
Right middle and left lower lobes + lingula	0	0	1	1
Right middle lobe + lingula	1	0	0	1
Right middle and left lower lobes	3	0	0	3
Right and left upper lobes	0	0	1	1
Right upper and left lower lobes	1	0	0	1
Left lower lobe + lingula	9	4	3	16
	58	20	34	112

from experience gained so far, in contrast to GREENFIELD, that it is not possible in this way to determine if a patient is amenable to conservative treatment or should be subjected to operation.

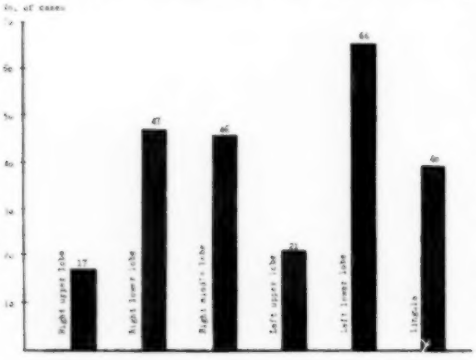

Diagram 1. The frequency of involvement of the various pulmonary segments in 112 cases of bronchiectasis.

Table 4 shows the sites of involvement and types of bronchiectasis in the patients studied. It is seen that the disease involved the right side in 37 cases (33 %), the left side in 46 cases (41 %), and both sides in 29 cases (26 %).

Dilatations were found exclusively in the bronchi of the left lower lobe in 16 %, the left lower lobe and the lingula in 14 %, and the right lower and middle lobes in 13 % of the cases.

Diagram 1 shows graphically the frequency of involvement of the individual pulmonary segments in the 112 cases. The left lower lobe was involved in 59 %, the lingula in 36 %, the right lower lobe in 42 % and the right middle lobe in 41 %, while the right and left upper lobe was the site of involvement in only 17 and 21 % of the cases, respectively.

The dilatations were cylindrical in 58 cases (52 %) and purely saccular in 20 cases (18 %), while 34 patients (30 %) showed a combination of the two types. Cylindric dilatations were observed both in the major and minor bronchial branches, *i. e.* both proximally and in the more peripheral portions. Saccular bronchiectases were invariably situated terminally in such a manner that there was no contrast medium peripherally to the pockets. The dilatations were often situated very close to the thoracic wall. Owing to similar observations by other writers, it has been believed up to now that saccular dilatations were invariably localized to the terminal bronchioles.

REID (1950) studied the bronchial subdivisions in bronchiectasis both bronchographically and by macroscopic and microscopic examinations of specimens removed at operations. Under normal conditions, about 17 subdivisions between the hilum to the periphery may be observed. No definite reduction in this number could be demonstrated in cylindric ectasia, whereas the number of bronchial subdivisions was considerably reduced (to about 5) in the presence of saccular dilatations. These observations suggest that saccular dilatations are localized to the proxi-

mal branches and not to the terminal bronchioles. The results of the present study were in complete agreement with REID's observations (Fig. 7 c).

The affected areas frequently revealed bronchi filled with secretion. and alveolar filling was never observed in the atelectatic portions. Owing to fibrosis and shrinkage, both ectatic and normal bronchial branches were often displaced from their normal positions.

A comparison between the bronchograms and operative findings showed good agreement. In one patient, the bronchogram revealed defective contrast filling of the left side due to marked secretion, but the segments filled with contrast medium revealed distinct saccular dilatations both in the upper and lower lobes. At operation, only the upper lobe was removed, because both visual and tactile examination of the lower lobe seemed to indicate normal conditions. Owing to the persistence of clinical signs, however, the lower lobe had to be removed 4 years later, and the macroscopic examination of the specimen then showed distinct ectasia.

In two other patients, the surface and consistency of the lung seemed normal, but both the cut surface of the specimen removed and the subsequent histologic examination showed distinct dilatations.

In the remaining 63 patients, operation revealed more or less pronounced adhesions, and the pulmonary tissue was firm and infiltrated or, sometimes, shrunken and atelectatic. In all these cases, the cut surface of the specimen removed, as well as histologic examination, fully confirmed the extent of the bronchiectatic process as previously observed in the bronchogram.

SUMMARY

The chest roentgenograms of 112 patients with verified bronchiectasis were analysed. Increased pulmonary markings were found in 85 %, honeycomb-like structures in 43 %, atelectasis in 31 %, and pleural changes in 47 %, while a normal appearance was found only in 7.1 % of the cases. The importance of the signs of bronchiectasis in the conventional film is discussed but it is pointed out that a definite diagnosis can be made only by bronchography. A comparison between the bronchograms and operative findings showed complete agreement as ergards the type and extent of the changes.

ZUSAMMENFASSUNG

Die Thoraxfilme von 112 Patienten mit verifizierten Bronchiektasien wurden analysiert. Vermehrte Lungenzeichnung wurde bei 85 % gefunden, honigwabenähnliche Schatten bei 43 % und Atelektase bei 31 %. 47 % der Patienten hatten pleurale Veränderungen. Ein völlig normales Röntgenbild lag nur bei 7.1 % der Patienten vor. Die Bedeutung des Zeichens von Bronchiektasien in dem konventionellen Film wird diskutiert aber es wird hervorgehoben, dass eine endgültige Diagnose nur durch die Bronchographie gestellt werden kann. Ein Vergleich zwischen den Bronchogrammen und den Operationsbefunden zeigte völlige Übereinstimmung bezüglich des Aussehens und der Ausbreitung der Erweiterungen.

RÉSUMÉ

Les radiographies thoraciques de 112 malades atteints de bronchiectasies verifiées ont été examinées. On a trouvé une augmentation des ombres pulmonaires dans 85 % des cas, des opacités en nid d'abeille dans 43 %, et une atélectasie dans 31 % des cas. 47 % des malades présentaient des signes d'atteinte pleurale. On n'a trouvé une image thoracique parfaitement normale que chez 7.1 % des malades. L'importance des signes de bronchiectasie dans le film conventionel est discutée, mais on fait pointer que le diagnostic ne peut être posé avec certitude que grâce à la bronchographie. La comparaison entre les bronchographies et les constatations opératoires a montré une concordance complète en ce qui concerne l'aspect et l'étendue des dilatations.

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STUDIES ON THE UPTAKE OF Fe^{59} IN RAT EMBRYO, PLACENTA, UTERUS AND MAMMARY GLAND

by

Gösta Magnusson, Ingmar Bergström and *Erik Odeblad*

Iron is an important element in the newborn mammal. Its uptake from the maternal organism during the fetal period is therefore of considerable interest. Using a Geiger-Müller counter, POMMERENKE et coll. (2) in 1942 demonstrated a high uptake of Fe^{59} in the red blood cells and liver of human embryo after the peroral administration of the isotope to the mother. In 1951, CAMPBELL and NYLANDER (1) studied the placental transfer of Fe^{59} in the rat by the technique of track autoradiography. They found a great number of tracks in the visceral yolk sac epithelium, while the allantoic part of the placenta showed comparatively few.

The scope of this investigation was to make extended observations of the uptake of Fe^{59} in the rat embryo, placenta and mammary gland by means of scintillation counting and apposition autoradiography. We feel that the method described is more easy to handle and more free from artefacts than the methods used in previous studies.

Experimental. Two pregnant rats were injected subcutaneously on the 20th day of gestation with 200 μC Fe^{59} per kg of body weight. The amount of carrier iron administered was 3.6 mg/kg body weight. 1, 3 and 5 days after injection, the embryos, placentas and mammary glands were removed either by Cesarean section or after killing the animals. A newborn rat, whose mother was given the isotope 7 days before death,

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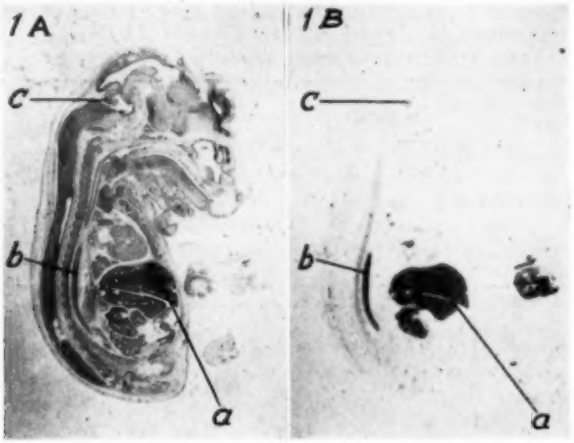

Fig. 1. Median sagittal section through embryo, and corresponding autoradiograph. Fe^{59}, which was administrated to the mother 1 day before death, is localized to the liver (a), the blood (b) and the choroid plexus (c). Magnification 3 ×.

and the mother's mammary gland, was also examined. The material was fixed in absolute methanol, containing 15 per cent formalin, for 48 hours. Embedding in paraffin and sectioning in 10 μ sections were then carried out. The sections were mounted on glass slides and deparaffinized in xylene. Apposition autoradiography was then performed, using Gaevert Dentus Rapid film, which was pressed directly against the slides, in iron screw presses. After exposure during 40 days, the sections and films were separated. The sections were stained with hemalum-eosin, and the films developed for 6 minutes in Gaevert 209A developer at + 19° C. After fixing, washing, and drying, the fog silver on the reverse side was removed with an excess of Farmer's solution. The resolution of the autoradiographs appeared to be about 20 μ. On analysis, the autoradiographs were compared in the microscope with the corresponding sections. The density of the film was nearly proportional to the exposure with the beta rays of the energy employed.

The radioactivity was measured with a scintillation counter with defined geometry in the tissues of the embryo and placenta, 1, 3 and 5 days, and of the mammary gland, 1 and 7 days after injection of the isotope, and compared with a radio-iron standard.

Results and discussion. The results are given in Tables I and II and exemplified in Figs. 1 to 5.

As seen in Table I, the fetus contained larger amounts of the radioisotope than the placenta at all the intervals selected. The mammary gland was found to accumulate much radio-iron 7 days after its administration. It is uncertain, if this uptake is correlated with lactation. Table II shows a high uptake of Fe^{59} in the blood and liver and moderate incorporation in the choroid plexus of the fetus and yolk sac placental tissue at all points of time observed. High accumulation of the radio-iron was detected where endochondral ossification occurred in the cartilage, which otherwise showed a low uptake of the radio-isotope (Fig. 3). In the embryos with longer observation times (3 to 7 days) the tissues in general showed detectable amounts of Fe^{59} in the autoradiographs (Fig. 2). The structural localization of the isotope in the liver was impossible to study owing to insufficient resolution of the autoradiographic method employed. A high content of Fe^{59} was seen in the mammary gland situated in the epithelium of the alveolar acini, 5 days after the injection (Fig. 5).

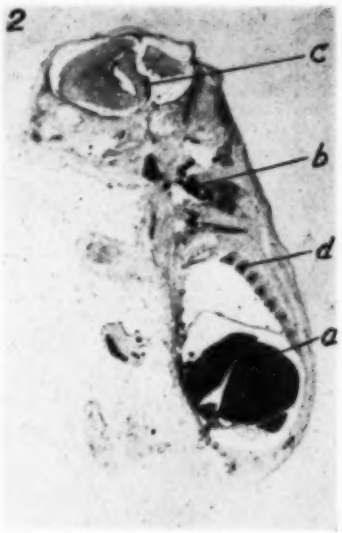

Fig. 2. Autoradiograph of embryo, showing the high uptake of radio-iron in the liver (a), the blood (b), the choroid plexus (c) and ossification zones in the cartilage of the ribs (d). The tissues in general accumulate detectable amounts of Fe^{59}, given to the mother 3 days earlier. Magnification 3 ×.

Table I

The radioactivity of fetus, placenta and mammary gland (millimicrocurie per gram)

	Time after injection of Fe^{59}			
	1 day	3 days	5 days	7 days
Fetus	87 ± 2	58 ± 3	109 ± 4	
Placenta	57 ± 2	42 ± 5	68 ± 1	
Mammary gland	25 ± 3			98 ± 5

With the techniques used in this work the previous findings have been verified, and additional findings made. The high uptake of Fe^{59} in connection with endochondral ossification in cartilage is probably due to the presence of growing capillaries. Rearrangement of the radio-isotope distribution could not be found with certainty during intervals of ex-

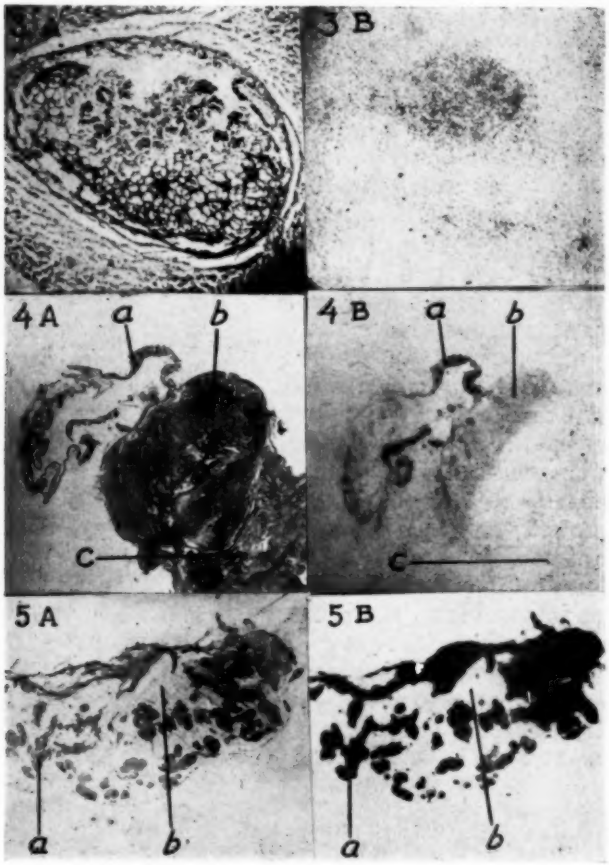

Fig. 3. Endochondral ossification in cartilage. High density is seen in the corresponding part of the autoradiograph 3 days after injection. Magnification 45 ×.

Fig. 4. Section and autoradiograph from placenta. High incorporation of Fe^{59} in yolk sac placenta (a) and moderate uptake in the allantoic part of placenta (b). No detectable amounts of the radio-iron in uterus (c) 1 day after injection. Magnification 4 ×.

Fig. 5. Section and autoradiograph from mammary gland. Large amounts of Fe^{59} in the epithelium of alveolar acini (a), no radio-iron in the connective tissue (b). Observation time: 5 days. Magnification 6 ×.

amination, probably owing to observation time being too short. The high uptake of Fe^{59} in the mammary gland is remarkable, because the content of iron in colostrum and mother's milk is known to be very low.

Table II

Presence of Fe^{59} in certain organs at different time intervals, studied by means of autoradiography

Organ	Time after injection of Fe^{59} 1 day	3 days	5 days	7 days
Embryo:				
blood	+++	+++	+++	+++
liver	+++	+++	+++	—
nervous system	0	+	+	—
choroid plexus	++	++	—	—
lungs	—	+	+	+
intestine	0	+	+	—
thymus gland	0	—	—	—
eye	0	—	—	—
musculature	0	+	+	+
cartilage	+	+ to +++	+ to +++	+ to +++
Fetal placenta:				
yolk sac placenta	++	++	++	—
allantoic placenta	+	+	+	—
Maternal placenta and uterus	0	0	—	—
Mammary gland	+	—	+++	—

0 = no detectable amounts of Fe^{59}
+ = small amounts of Fe^{59}
++ = moderate amounts of Fe^{59}
+++ = large amounts of Fe^{59}
— = not observed

SUMMARY

The uptake of Fe^{59} in the rat embryo, placenta and mammary gland in the last part of the gestation period was studied by means of scintillation counting and apposition autoradiography 1, 3, 5 and 7 days after its subcutaneous injection in the mother. High amounts of radio-iron were found in the fetal blood, liver, choroid plexus, endochondral ossification zones, yolk placenta and maternal mammary gland.

ZUSAMMENFASSUNG

Die Aufnahme von radioaktivem Eisen (Fe^{59}) wurde bei Ratten am Embryo, an der Plazenta und am Mammargewebe während des letzten Abschnittes der Graviditet studiert. Die Untersuchungen wurden mittels Szintillationsrechnung und Autoradiographie 1, 3, 5 und 7 Tage nach subkutaner Injektion am Muttertier gemacht. Hohe Konzentrationen von radioaktivem Eisen wurden im Blut, in der Leber, im Chorioidalplexus und in der endochondralen Ossifikationszone des Embryos beobachtet, ausserdem in der Plazenta des Gelbensackes und im Mammargewebe des Muttertieres.

RÉSUMÉ

Les auteurs ont étudié l'accumulation du fer radioactif dans l'embryon, le placenta et le tissu mammaire de la femelle du rat pendant la dernière partie de la gravidité. L'examen a été fait avec un compteur à scintillation et par autoradiographie 1, 3, 5 et 7 jours après l'injection sous-cutanée à l'animal gravide. On a trouvé une forte concentration de fer radioactif dans le sang, le foie, les plexus choroïdes, les zones d'ossification enchondrale de l'embryon, le placenta, le corps jaune et le tissu mammaire maternels.

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CAVERNOUS HEMANGIOMA ASSOCIATED WITH PHLEBOLITHS IN THE MASSETER MUSCLE

by

A. Schwartz and *N. Salz*

Cavernous hemangiomas situated on skin surfaces are of fairly frequent occurrence but when lying deep in the muscular structures of the face are of considerable rarity. The diagnosis of a deep-seated tumour of this nature can scarcely be made with any degree of certainty on a purely clinical basis. The presence of phleboliths, as determined by roentgen examination, will, however, suggest the correct diagnosis. Because of the relative rarity of the condition in this particular site and because the roentgen investigation was able to give the clinician an accurate diagnosis of a tumour, which had previously been misdiagnosed, we feel it worth while to report the following case.

Fig. 1. Phleboliths in the masseter muscle.

I. P., a Jewish male, aged 17, was admitted to the Surgical Clinic of the University Hospital complaining of a painless mass in the region of the left cheek. According to the history, the mass had been present since birth and apparently had not increased in size. At the age of 7, a diagnosis of lymphangioma was made and radium therapy given without apparent effect. At the age of 13, he again received radiation therapy which was also ineffective. As a result of this lack of response to therapy, he was referred to the Department of Surgery.

An examination at this time revealed a soft, slight fluctuating, non-tender mass, approximately 4 cm in diameter, lying in the parotid region just above the angle of the jaw. The tumour was well demarcated and the overlying

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skin freely movable and of normal appearance. More deeply, and particularly from the buccal surface, two hard movable masses, about 4 mm in diameter, could be palpated. It was assumed, therefore, that these were stones obstructing Stenon's duct, at least partially, and that the mass was a resulting cystic dilatation of the parotid gland. A roentgen examination was carried out in order to locate the stones more accurately. The films obtained (Fig. 1) suggested that the doubtful opacities were in the nature of phleboliths rather than stones and accordingly compatible with a diagnosis of cavernous hemangioma.

Operation was undertaken under general anaesthesia. The area was widely exposed by a curved incision placed behind the angle of the jaw. The mass was found to lie anteriorly to the parotid gland deep and within the fibres of the masseter muscle. The tumour, an extremely vascular one, was enucleated by blunt dissection and the incision closed.

Pathologic examination revealed widely dilated vascular channels.

Treatment in this condition being dependent on adequate diagnosis, every means should be employed to this end. Earlier roentgen examination in this young subject would have avoided repeated ineffective and possibly harmful courses of radiation therapy.

SUMMARY

A case of cavernous hemangioma within the masseter muscle, diagnosed roentgenologically, is reported.

ZUSAMMENFASSUNG

Bericht über ein röntgenologisch diagnostiziertes kavernöses Hämangiom im M. masseter.

RÉSUMÉ

Présentation d'un cas d'hémangiome caverneux du muscle masséter diagnostiqué radiologiquement.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR: KJELD ANDERSEN), BISPEBJERG HOSPITAL, DENMARK

AN INTERHEMISPHERICALLY SITUATED HAEMATOMA

Case Report

by

H. H. Jacobsen

The clinical picture of a subdural haematoma is in some cases relatively typical, while in others it is difficult or impossible to make a definite diagnosis solely by clinical methods. A correct diagnosis is, however, of great importance to ensure adequate surgical treatment. Many still employ exploratory drilling for the diagnosis. It is true that the subdural haematoma has certain sites of predilection: above the convexity, in the Sylvian fissure, or on the basal surface of the frontal lobe. In order to arrive at a correct diagnosis, it may, however, be necessary to drill several holes, since the haematoma may be situated practically anywhere. It is also often impossible to decide clinically between whether a condition is one of subdural haematoma or intracerebral haemorrhage. By means of angiography, however, it is possible to differentiate without difficulty between extracerebral and intracerebral haemorrhage and, furthermore, the former may be localized exactly. The roentgen diagnosis of post-traumatic intracranial haemorrhages has been described by WICKBOM and several other authors. The writer has, however, seen no description of a haematoma situated between the hemispheres, which is the reason for the publication of the following case report.

A 23-year-old man was admitted five days after a head injury with initial unconsciousness. Ophtalmoscopy showed that the right optic disc was somewhat blurred. Paresis of the left leg; Babinski test positive on the left side.

Angiography was carried out through the right internal carotid artery. The pericallosal artery lay just to the left of the mid line. Its central and posterior part was stretched and depressed slightly basally. The vessels on the medial side of the hemisphere were displaced from the mid line, so that an avascular, longish, relatively narrow area

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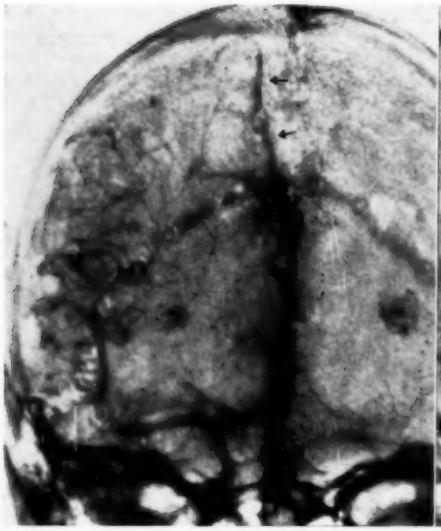

Fig. 1. Angiography on the right side. Avascular area along the falx cerebri (arrows).

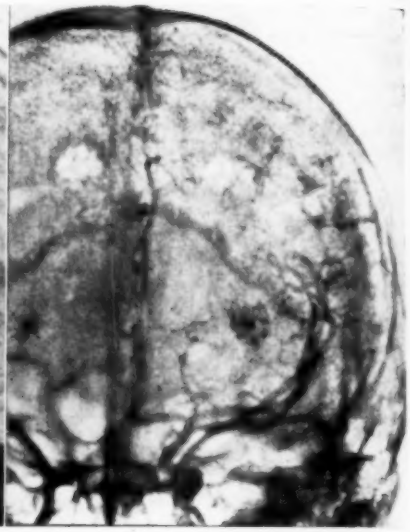

Fig. 2. Angiography on the left side.

was created along the falx cerebri, which, in the a. p. films appeared as roughly triangular with its base directed upwards (Fig. 1).

Angiography through the left internal carotid artery showed no displacement of the medial margin of the hemisphere from the mid line. The pericallosal artery, however, described a small limited curve towards the left (Fig. 2).

An operation was performed the day after the investigation. Through a bur hole 5 cm behind the vertex and just to the right of the mid line, a subdural haematoma, stretching across the precentral area and down to the corpus callosum, was found. It was removed.

Six days after the operation the changes in the right optic disc had disappeared. Nine days later, the paresis of the left foot had decreased considerably, and the patient was discharged.

SUMMARY

A case of a haematoma, situated interhemispherically, is described.

ZUSAMMENFASSUNG

Bericht über ein interhemisphärisch gelegenes Hämatom.

RÉSUMÉ

Présentation d'un cas d'hématome interhémisphérique.

REFERENCE

WICKBOM, I.: Angiography in Post-Traumatic Intracranial Haemorrhages. Acta radiol. 32 (1949), 249.

FROM RADIUMHEMMET (DIRECTOR: PROF. SVEN HULTBERG), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

THE INCIDENCE OF CANCER OF THE UTERINE CERVIX AND CANCER OF THE BREAST IN SWEDEN

by

C.-O. Segerdahl

It has long been desirable to obtain a correct picture of the incidence of different types of cancer in Sweden and of the temporary variation of this incidence. Such knowledge, combined with information about the population development in the ages exposed to cancer, provides a good illustration of the claims likely to be made on cancer therapeutics in Sweden in the near future. A comparison with conditions prevailing in other countries, especially Denmark, where the Danish Cancer Registry is a good example in this field, might also furnish information about differences in the incidence of various types of cancer in relation to geographic, social and transport conditions, etc.

Material

In Sweden, as in Denmark and Norway, treatment arrangements are very suitable for making statistic studies of cancer of the uterine cervix. In these countries, this type of cancer has, for several decades, been treated almost exclusively radiologically or at the radiologic clinics, so that the primary statistic material for further studies is well concentrated. The material used in this investigation covers the period 1920—1949 inclusive, being assembled from the radiologic clinics in Stockholm, Gothenburg and Lund—Malmö as well as from the General Lying-in Hospital in Stockholm, which earlier treated a few cases radiologically although no longer does so. These series, comprising altogether 10,863 cases, have already been published in another connection (4). They are used, however, in this paper, because another age grouping is concerned,

some further investigations on the material are presented and, further, in order to compare the development of the incidence of cancer of the uterine cervix in these cases with the corresponding incidence for cancer of the breast.

As regards cancer of the uterine cervix, the study covers the whole of Sweden. A regional division of the material would have caused substantial difficulties as, although the regions are always strictly defined, several variations occurred in the acceptance regions of the different clinics during the time studied.

When it was decided to extend the investigation to embrace cancer of the breast, the assembling of the primary material presented a much greater problem. This type of cancer is treated surgically in practically all hospitals throughout the country, and a complete investigation would have necessitated going through a greater number of records. As many different systems are used, a complete perusal of all these hospital records which did not at the same time include the gathering of statistic information from all the records, on punch-cards for example, would have meant an amount of work out of all proportion to the results obtained.

It was therefore decided to make a trial in the first place with the conditions existing in Stockholm. Even so, a great deal of work was required as it was necessary to go through the records at all the hospitals concerned in order to select the individual cases of cancer of the breast required. The hospitals investigated were the state hospitals Karolinska Sjukhuset (Radiumhemmet) and Serafimerlasarettet with patients from Stockholm and the provinces, the municipal hospitals with patients almost solely from Stockholm and, finally, some private clinics with patients from different parts of the country. The municipal hospitals were the Eira, Ersta, Sabbatsberg, St. Erik, St. Göran, Stigberget, Södersjukhuset (including Maria) and Åsö hospitals; the private hospitals consisted of the Betaniahemmet, Röda Korset and Sophiahemmet hospitals. In every case the responsible authorities showed themselves kindly disposed towards the investigations and gave permission for their records to be examined for the material required.

A few cases may have been missed from small private hospitals not included. Experience shows that such cases are very difficult to trace in the records available at these hospitals. The total number of such cases should, however, be negligible as roentgen or radium treatment in connection with operation is, at these hospitals, normally given at the Radiumhemmet, where they are also registered.

It is possible that a few cases from Stockholm have been treated outside Stockholm. As the scale of municipal hospital charges is, however, so arranged in Sweden that the fees are much higher for patients in a region other than that in which they are domiciled, such cases must be

extremely rare and can therefore be disregarded. They would also be counterbalanced by those few which, in spite of the great care exerted, may have crept into the investigation from places outside Stockholm. In some cases, a temporary Stockholm address might have been given and noted in the records.

Summing up, the possibilities of error mentioned above are unimportant and without influence on the frequency figures calculated from the material.

The series of cases collected comprise all cases found which received their first treatment for cancer of the breast during any one of the years 1929—1949 inclusive.

It proved convenient to prepare an individual card for each case in the whole material in order to lighten the work of tracing cases originating from different hospitals but obviously indicating the same individuals. The cards were sorted in turn into name-order, birthday and birth-year order. In this way it was possible to weed out duplicate names and some cases in which, in spite of small differences in names, the same individuals were obviously indicated. It even proved possible to locate some other cases in which, although differences in name and year of birth existed in the statements from different hospitals, duplication of the same individuals had taken place. When duplication was discovered, only one (the oldest) card was retained in the material. The material originally consisted of 4,886 cards. Of these, 1,124 were removed because of similarity in names, a further 55 on account of similarity in birthdays and after comparison of names, and, finally, 37 more at a last extra control. This left a final material consisting of 3,670 cases, of which 3,651 were females and 19 males. This investigation is chiefly concerned with the female cases.

Although a great deal of labour is spent on keeping the records of cases in the different hospitals, our experience was that, especially in so far as old series are concerned, defects exist. The registration systems varied considerably in different hospitals; erroneous statements were obtained and had to be corrected. In short, in spite of the ready courtesy extended at all hospitals visited, and the generous help from those well acquainted with the details examined, the method of investigation it was necessary to use proved extremely laborious.

Morbidity in the two types of cancer investigated

It was desired to investigate both the incidence and temporary variation of the incidence of cancer of the uterine cervix and cancer of the breast. For this reason it was necessary to arrange the material obtained into age groups as well as into groups according to the calendar year

when the cancer was first diagnosed. These groups are presented in Table 1 for cancer of the uterine cervix and in Table 2 for cancer of the breast in females.

Table 1

Number of Cases of Cancer of the Uterine Cervix. Sweden

Calendar years	Age in years attained during the calendar year when cancer of the uterine cervix was first observed														Total
	—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89	
1920—24	1	15	63	104	120	160	148	98	122	65	26	7	5	2	936
1925—29	—	27	79	120	182	181	210	147	114	93	50	18	3	3	1,227
1930—34	3	40	104	207	253	279	254	200	140	105	56	25	5	—	1,671
1935—39	16	46	117	209	277	317	290	282	165	127	62	43	8	1	1,960
1940—44	6	66	151	260	341	363	363	303	205	141	76	38	15	4	2,332
1945—49	14	69	168	327	409	418	436	334	227	174	104	47	6	4	2,737
														Grand total	10,863

Table 2

Number of Cases of Cancer of the Breast. Stockholm

Calendar years	Age in years attained during the calendar year when cancer of the breast was first observed														Total
	—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89	
1929—34	5	9	19	40	88	133	108	90	107	84	69	34	11	8	805
1935—39	—	4	13	42	80	116	97	116	105	93	62	51	20	5	804
1940—44	—	2	21	47	107	124	111	119	122	110	98	60	30	5	956
1945—49	—	9	17	53	98	136	145	132	140	106	121	77	33	19	1,086
														Grand total	3,651
1929—49	5	24	70	182	373	509	461	457	474	393	350	222	94	37	3,651

The few cases of cancer of the breast observed amongst men do not call for any further division. It seems sufficient to state that the male cases are about 0·5 % of the female cases whilst the corresponding figure in the Danish material is 1·1 % (3). The sex proportion (of men to women) is not the same in the whole Danish population, from which the Danish material was obtained, as in the population of Stockholm. The proportion varies from age-group to age-group, and it is difficult to obtain a satisfactory average proportion. In ages above 45 years, when most cases occur, the proportion in Denmark in the years 1943—1947 was 0·921 : 1 while in Stockholm in 1945 it was 0·732 : 1. This difference tends to eliminate part of the variation between the frequencies, although only a small part of it. However, the absolute number of cases observed is so small here that it is impossible to draw any extensive conclusions from it.

The figures obtained from the annual population totals of women exposed to risk within the two materials considered are given in Tables 3 and 4. For all Sweden, they have been taken from the figures published by the General Statistical Bureau, and for Stockholm, from the figures published by the Statistic Office of the City of Stockholm, the latter figures embracing the population within the administrative area of Stockholm City. The population of Stockholm is given as at 1 November from the end of 1946 and not as at 31 December, this resulting from the system of population registration in Stockholm. We have used the official figures as they are, because the difference between the two dates may be safely ignored for the purposes of this investigation.

The figures in Tables 3 and 4 thus comprise five times the average annual population in the different five-year periods for each of the age-groups observed (Note: For Stockholm City the first line comprises 6 calendar years, and the figures correspondingly give six times the average population in the different age-groups).

Table 3

The Number of Years Exposed to Risk for Women of Different Age-Groups for Certain 5-year Periods. Sweden

(Figures in Thousands)

Age-group	20—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89
5-year period														
1920—24	1,293	1,177	1,081	999	897	805	691	679	630	514	402	282	167	72
1925—29	1,346	1,245	1,140	1,051	971	868	774	656	632	563	430	298	170	74
1930—34	1,380	1,313	1,218	1,116	1,027	944	837	735	611	565	468	316	178	73
1935—39	1,318	1,365	1,301	1,205	1,099	1,003	913	799	686	547	470	344	189	77
1940—44	1,340	1,311	1,355	1,288	1,189	1,078	975	875	749	618	459	346	206	82
1945—49	1,210	1,355	1,321	1,359	1,284	1,180	1,054	939	824	681	525	344	211	91

Table 4

The Number of Years Exposed to Risk for Women of Different Age-Groups for Certain Periods. Stockholm

(Figures in Thousands)

Age-group	20—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89
5-year period														
1929—34	183	190	170	152	140	122	101	82	67	59	45	27	13	5
1935—39	143	173	161	143	128	118	103	84	67	51	41	28	13	5
1940—44	155	166	175	161	142	128	117	101	81	61	43	31	17	6
1945—49	143	180	171	175	161	143	128	114	98	75	53	33	19	8
1929—1949	623	708	677	630	572	511	449	381	312	246	183	119	62	23

As the figures stated are proportionate to the average population, it is possible to make some interesting observations from Tables 3 and 4. Table 3 shows that in Sweden the age-groups have been steadily increasing in size during the calendar years observed, as far as the middle and higher age-groups are concerned. In the younger age-groups, there has been a reversal as the age-group 20—24 years reached its maximum during the years 1930—1934. This maximum then advances through age and calendar year groups so that the age-group 35—39 years attains its maximum during the period 1945—1949. These facts are of special interest in regard to the absolute number of cancer cases as showing the large population increase in the middle and higher age-groups, where the greatest incidence of cancer is to be expected.

On account of the high rate of immigration into Stockholm from the provinces, the population development is somewhat different from that of the whole country. Table 4 shows, however, that some of the same features may also be observed for Stockholm City where there has been a large increase of the population in the middle and higher age-groups whilst the number in the younger age-groups has stagnated or decreased.

Finally, Tables 5 and 6 give the observed figures of the incidence of cancer (morbidity intensity) within the different age-groups during the various periods of observation. These figures are the quotients between the corresponding figures in Tables 1 and 3 and Tables 2 and 4, respectively.

The results show that the incidence of cancer of the uterine cervix has been consistently and heavily increasing during the period of observation whilst that of cancer of the breast has been fairly constant apart from the ages above 70 where a certain increase seems to be noticeable.

Table 5

Incidence (Intensity of Morbidity) of Cancer of the Uterine Cervix in Certain Age-Groups for Different 5-year Periods. Sweden

Per 10,000

Age-group	20—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89
5-year period														
1920—24	0·01	0·13	0·58	1·05	1·34	1·99	2·14	1·44	1·94	1·26	0·65	0·25	0·30	0·28
1925—29	0·00	0·22	0·69	1·14	1·87	2·08	2·71	2·24	1·80	1·65	1·16	0·60	0·18	0·41
1930—34	0·02	0·30	0·85	1·85	2·46	2·96	3·04	2·72	2·29	1·89	1·20	0·79	0·28	0·00
1935—39	0·12	0·34	0·90	1·73	2·52	3·16	3·18	3·53	2·40	2·32	1·32	1·25	0·42	0·13
1940—44	0·04	0·50	1·11	2·02	2·87	3·37	3·72	3·46	2·74	2·28	1·66	1·10	0·73	0·49
1945—49	0·12	0·51	1·27	2·41	3·19	3·54	4·14	3·56	2·75	2·55	1·98	1·37	0·28	0·44

Diagram 1 provides a comparison between the incidence of cancer of the uterine cervix in Sweden according to this material and the Danish experience for the years 1943—1947 inclusive (2). In spite of the heavy increase in the morbidity rate for this type of cancer in Sweden, this

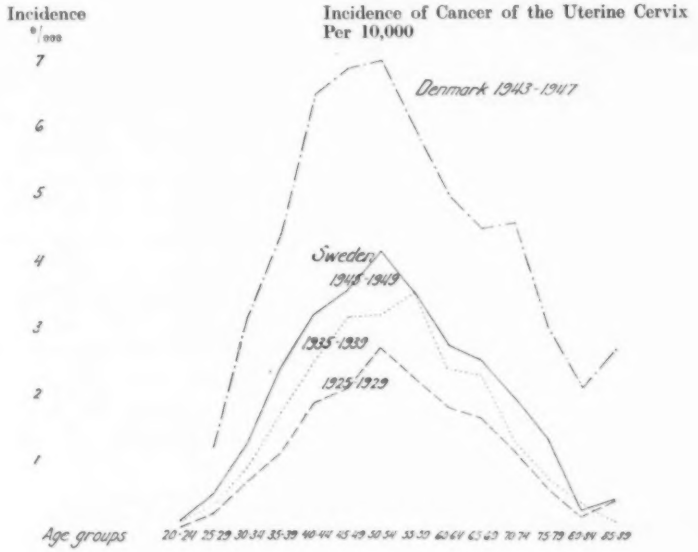

Diagram 1.

country is still far behind the Danish figures. Should development be such that the Danish experience is repeated, a further heavy increase in the incidence of this type of cancer in Sweden is to be expected.

The question was also considered as to whether the low figures in Sweden might not be partly attributed to the fact that many cases of cancer of the uterine cervix were not recorded, more so in the earlier days than now, with special consideration of the problems caused by sparse population and difficult and expensive travel conditions in Northern Sweden. A simple study of the population figures for the sparsely inhabited areas at once showed that, even assuming cases had been missed, the population involved was by no means sufficient to explain either the variations of the Swedish frequency figures or, compared to the Danish, their fairly low level. Furthermore, the medical services in these areas are now so well-organized (the railway journeys to radium clinics

being free of charge to the patient) that this question may safely be ignored.

There has been no division of the material into married and single women in this study as in the Danish study (2).

Table 6 shows that, for cancer of the breast, there has been hardly any change in the incidence of this disease, apart from some higher ages, during the period observed. For this reason, we have also calculated a rate of morbidity, based on the entire material, in order to obtain as much smoothing of the effects of random fluctuations as possible.

Table 6

Incidence (Intensity of Morbidity) of Cancer of the Breast in Certain Age-Groups for Different Periods. Stockholm

Per 10,000

Age-group	20—24	25—29	30—34	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	75—79	80—84	85—89
Period														
1929—34	0·27	0·47	1·1	2·6	6·3	10·9	10·6	10·9	16·0	14·1	15·2	12·6	8·4	16·4
1935—39	—	0·23	0·81	2·9	6·3	9·9	9·5	13·8	15·7	18·4	15·0	18·3	15·2	10·8
1940—44	—	0·12	1·2	2·9	7·5	9·7	9·5	11·8	15·1	18·0	22·7	19·5	17·9	8·8
1945—49	—	0·50	1·0	3·0	6·1	9·5	11·3	11·6	14·3	14·2	22·8	23·3	17·6	24·7
Total period														
1929—49	0·08	0·34	1·03	2·89	6·52	9·96	10·3	12·0	15·2	16·0	19·1	18·7	15·2	16·2

In regard to the ages above 70, it should be mentioned that the remarkable increase in incidence of cancer of the breast is probably attributable to the fact that the material only includes cases treated in hospitals. While many such cases were earlier not treated in hospitals, elderly patients are now admitted in these institutions to a very much greater extent than before.

The Danish study (2) does not indicate any great difference in incidence between urban or rural districts in cancer of the breast as is the case in cancer of the uterine cervix. It might therefore be expected that the Stockholm material for cancer of the breast would give a fairly accurate picture of conditions throughout Sweden. More accurate knowledge on this point will perhaps be obtained when the results of the 1953 cancer registration in Sweden are available.

The Danish experience of a temporary standstill in the increase of the incidence of cancer of the breast during the menopause is repeated in the Stockholm material.

In marked contrast to the findings in cancer of the uterine cervix, the Swedish figures on the incidence of cancer of the breast agree extremely well with the Danish as is seen from Diagram 2. The Danish figures given have been taken from ref. 3.

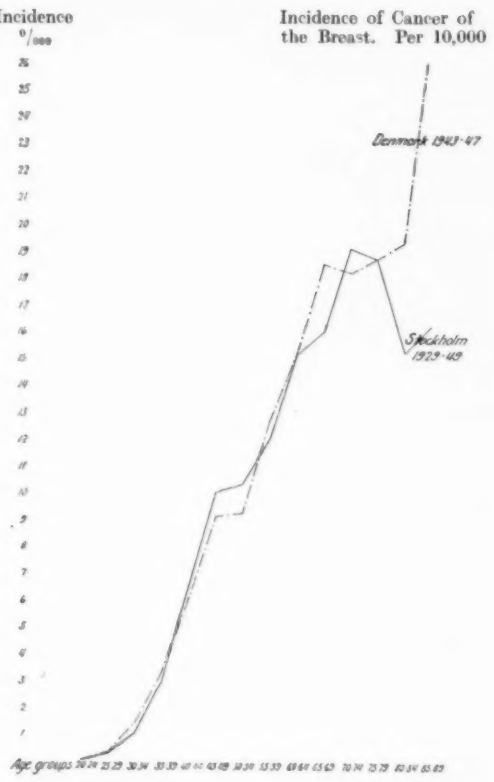

Diagram 2.

It should be noted that the stringent check on cancer cases provided by the mortality statistics in the Danish Cancer Registry has not been available in this investigation; this control enables even those cases not treated in hospital to be accurately calculated. It is considered that such cases may be safely disregarded in the Stockholm material; it is stressed, however, that too hard-pressed conclusions should not be drawn from the figures for the higher ages.

As far as it has been possible to discover from the literature, the Swedish material presented covers the longest period for which similar figures have been collected and published. It is therefore of special interest to observe the incidence over a period of the two types of cancer studied. The hypothesis has been suggested in some quarters that an increase in the rate of cancer of the uterine cervix may be correlated with a decrease in the rate of cancer of the breast. If such an hypothesis were to be proved, it would be of great importance in studies on the nature of cancer. The two types of cancer investigated in this investigation might then possibly be traced to one and the same principal factor, viz. hormonal conditions. It is not considered, however, that any categoric statement can be made on this point from this material as, for one of the types of cancer concerned the material refers to the country as a whole, and for the other to

Stockholm only. It would be necessary first to make an investigation of the cases of cancer of the uterine cervix in Stockholm only, in order to obtain exact information. Nevertheless, two facts should be considered in this connection. On the one hand, a fairly heavy increase in the rate of cancer of the uterine cervix in the country as a whole has been demonstrated, and may be compared with the Danish experience of increasing incidence of cancer of the uterine cervix with an increase in the size of cities (2), and, on the other hand, a fairly constant incidence of cancer of the breast in Stockholm. A consideration of these two observations strongly suggests that an increase in the incidence of cancer of the uterine cervix has not been accompanied by a decrease in the incidence of cancer of the breast.

Table 7

The Risk that a Woman of a Given Age Will, during the Remainder of her Life, Develop

At Age	Cancer of the Uterine Cervix Swedish Experience 1945—1949 (Mortality 1941—1945)	Cancer of the Breast Stockholm Experience 1929—1949 (Mortality 1931—1940)
	Risk in ‰	
20	11·8	42·8
25	11·8	43·3
30	11·6	43·8
35	11.1	43·9
40	10·0	43·1
45	8·5	40·7
50	6·9	36·9
55	5·0	33·2
60	3·5	29·0
65	2·4	23·8
70	1·4	19·0
75	0·7	13·6
80	0·2	9·0
85	0·1	7·0

The investigation has also served to throw some light onto a further interesting question. What are the chances that a woman of a given age will develop cancer of the breast or cancer of the uterine cervix during the remainder of her life? The material available in the previous investigation made it possible to calculate this probability for cancer of the uterine cervix in Sweden and for cancer of the breast for women in Stockholm only. The computation of the former has been based on the mortality rates of the female Swedish population for the period 1941—

1945 and the incidence of cancer of the uterine cervix during the years 1945—1949; the latter on the mortality of women in Stockholm 1931—1940 and the incidence of cancer of the breast in Stockholm 1929—1949. In the second case, the computation has thus been based on the entire material, as the incidence in cancer of the breast has not been observed to vary very much over a period of years. Consequently, the increase in incidence for ages above 70 is only partly accounted for, although this has no effect on the order of magnitude of the results.

The results for both types of cancer are given in Table 7. This table vividly illustrates the risks at different ages and also expresses in plain figures the predominance of cancer of the breast over cancer of the uterine cervix. When reading the table, however, it should be remembered that corpus, ovarian and vaginal cancers are not included in the material. It is worthy of note that while the risk of cancer of the breast for a woman in the 20—40 year period is about 4 times greater than the risk of cancer of the uterine cervix, the corresponding risk for a 60-year-old woman is 10 times greater, the proportional risk growing still greater with increasing age.

SUMMARY

The method employed in carrying out a statistic survey of the incidence of uterine cancer in the population of the whole of Sweden during the period 1920—1949 and of cancer of the breast in the City of Stockholm in the period 1929—1949, is described. It appears that a heavy increase in the incidence of the former, but little change in the incidence of the latter, has occurred. The risks of women in various age-groups developing these diseases is calculated and discussed.

ZUSAMMENFASSUNG

Die Methode wird beschrieben, die bei der Durchführung einer statistischen Untersuchung über die Häufigkeit des Uteruskarzinomes in der Bevölkerung von ganz Schweden während des Zeitraumes 1920—1949 und die des Mammakarzinomes in der Stadt Stockholm während des Zeitraumes 1929—1949 benutzt worden ist. Es zeigt sich, dass ein starker Anstieg der Häufigkeit des Ersteren, aber nur eine kleine Veränderung der Häufigkeit des Letzteren stattgefunden hat. Das Risiko für Frauen in verschiedenen Altersgruppen, diese Krankheiten zu bekommen, wird kalkuliert und besprochen.

RÉSUMÉ

L'auteur décrit la méthode employée pour faire une étude statistique de la fréquence du cancer de l'utérus sur la population de l'ensemble de la Suède pendant la période 1920—1949 et du cancer du sein dans la ville de Stockholm dans la période 1929—1949. Il ressort de cette étude qu'il s'est produit une forte augmentation de la fréquence du premier, mais peu de changement dans la fréquence du second. Le risque pour que des femmes de différents groupes d'age soient atteintes de ces affections est calculé et discuté.

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FROM THE GYNECOLOGICAL CLINIC (DIRECTOR: PROF. P. WETTERDAL), SABBATSBERGS SJUKHUS, KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

DETECTION OF BERYLLIUM BY MEANS OF THE Be^9 $(a, n\gamma)C^{12}$ REACTION

by

Erik Odeblad and *Giuseppe Nati*

If beryllium is irradiated with alpha particles of sufficient energy certain nuclear reactions take place. As a first step the compound nucleus C^{13} in an excited state is formed:

$$Be^9 + a^4 \rightarrow C^{13x}.$$

The compound nucleus may then be de-excited in several ways, of which the following are the most important:

$$C^{13x} \rightarrow \begin{cases} \rightarrow B^{12} + p - 7.2 \text{ MeV} & \text{(a)} \\ \rightarrow C^{12} + n + 5.6 \text{ MeV} & \text{(b)} \\ \rightarrow C^{12} + n + \gamma \text{ (4.4 MeV)} + 1.2 \text{ MeV} & \text{(c)} \\ \rightarrow C^{13} + 11.4 \text{ MeV (several } \gamma \text{ rays possible).} & \text{(d)} \end{cases}$$

If the energy of the incoming alpha particle does not exceed 11 MeV, reaction (a) is energetically excluded. Reaction (d) is, in our experience, relatively unimportant. The branching ratio between reaction (b) and (c) is such (DILLER and CROUCH 1954) that about 40 per cent of the events follow eq. (b) and 60 per cent eq. (c).

The reactions (b) and (c) which form one of the most common ways of producing neutrons, may be taken as a basis for the detection of beryllium due to the fairly high cross section (HALPERN 1949) and integrated yield (SEGRÉ and WIEGAND 1948). For the purpose of detecting beryllium, either the neutrons or the gamma rays of 4.4 MeV may be recorded. We found, by experience, that it was most convenient to record the gamma rays upon the bombardment of the sample with alpha particles from Po^{210}.

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Experimental

The experimental arrangement is shown in Diagr. 1. The 130 mC Po^{210} source (described earlier, ODEBLAD 1954) has been kept at a carefully measured distance from the target containing beryllium, because

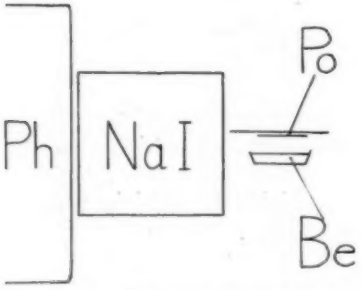

Diagram 1. The arrangement of the alpha source (Po^{210}), target (Be), scintillation crystal (NaI), and photomultiplier (Ph), for the detection of beryllium.

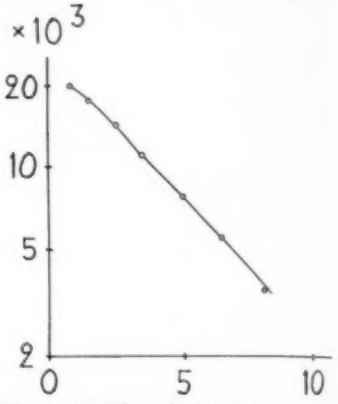

Diagram 2. The relation between the distance between the Po^{210} source and the specimen, in mm (abscissa) and the counting rate, in counts per min. (ordinate, logarithmic scale).

the distance influences the recorded counting rate. Care has been taken to avoid direct contact between source and specimen (see Diagr. 2).

By balancing the amplification of the pulses and the discriminator setting, it was possible to reduce the background while a large fraction of the pulses due to 4.4 MeV gamma rays was still recorded. The background was mainly due to the 0.81 MeV gamma rays which, to the extent of 0.001 per cent accompany the disintegrations of Po^{210}. The influence of various degrees of amplification of the pulses on the background and 4.4 MeV gamma counting rate is shown in Diagr. 3. With the pulse amplification commonly used, the background was about 30 counts per min.

The crystal was a cylindrical NaI(Tl) scintillator, 25 × 25 × 25 mm in size, connected with an E. M. I. 6,260 photomultiplier, operated at 1,300 volts. After proper amplification, the pulses were recorded continuously on an oscillograph screen for control of pulse height, and were counted with a scaler. The pulse height distributions from the 4.4 MeV gamma rays from the Be^9 (α, n γ)C^{12} reaction, the gamma rays from Na^{24} (2.76 MeV gamma line used for calibration), and from the back-

ground, are shown in Fig. 1. The pulse height distribution of the nuclear reaction is in agreement with the curve published by FITCH and RAINWATER (1953).

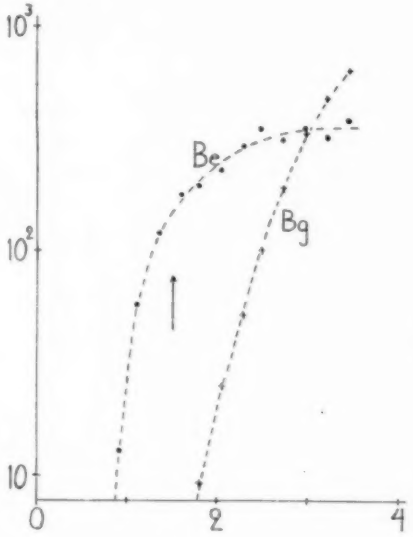

Diagram 3.

Fig. 1.

Diagram 3. Influence of pulse amplification (in arbitrary units) on the background counting rate (Bg) and the counting rate of the 4.4 MeV gamma rays from beryllium (Be). The polonium source present in both cases. The setting commonly used on the amplifier is indicated by an arrow.

Fig. 1. Pulse height distribution of the 4.4 MeV gamma rays from the Be^9 $(\alpha, n\gamma)C^{12}$ reaction (top). Na^{24} used for calibration, utilizing the 2.76 MeV gamma line (middle), and the background, including the Po^{210} gamma rays of 0.81 MeV (bottom) at the discriminator setting commonly used.

Results

1. Gamma ray yield from various substances irradiated. In order to investigate the specificity of the method for beryllium, a number of substances containing various elements were irradiated with the alpha particles from Po^{210}, the gamma rays counted, and pulse height distributions studied. Some results are shown in Table I. Other elements than beryllium giving an appreciable gamma ray yield are: boron, aluminum, magnesium and fluorine. Their pulse height distributions differ considerably from that of beryllium. All of these four elements are normally present in fairly small amounts in biologic samples. Sodium gives a small

yield and the biologically most important elements, hydrogen, carbon, nitrogen and oxygen seem to give a hardly detectable yield. By comparing the beryllium-containing tissue with a corresponding control preparation from normal tissue, the background gamma rays from the biologic material may always be accounted for sufficiently.

Table I

Gamma ray yield from various substances irradiated

Substance irradiated	Yield of gamma rays (counts per min.) at amplifier and discriminator settings commonly used	Mean error of B (six determinations)
Be	12,230	57
$BeCl_2$	1,403	41
$BeCO_3$	1,032	44
H_3BO_3	386	11
Al	112	3
LiF	110	10
NaF	67	6
Mg	30	5
$Na_2S_2O_5$	21	3
$Na_2HPO_4 \cdot 2H_2O$	20	4
NaCl	18	5
KCl	16	5
NaI	15	5
CaO	7	3
K_2CO_3	7	2
$(NH_2)_2CO$	6	3
$FeSO_4$	6	3
Dried blood plasma	5	3
Dried blood cells	4	4

Our measured yields from various elements seem to be in fairly good agreement with a large number of papers published in the Physical Review during the last few years.

2. The relation between the number of counts and the beryllium content. Human plasma and red blood cells were mixed with beryllium chloride in known amounts, dried and studied. The results are shown in Diagr. 4. There seems to be a roughly linear relationship between the amount of beryllium present in the sample and the number of counts per min. recorded.

3. Influence of the kind of tissue on the recorded counting rate. Because the amount of dry substance varies from one tissue to another, the number of beryllium atoms reached by the incoming alpha particles under bombardment is expected to vary. Some results from various kinds of tissue are shown in Table II.

4. Comparison between the counting rate recorded in dried and ashed blood. The same reason as mentioned in the preceding paragraph increases the probability that the alpha particles will hit beryllium atoms if the samples are ashed. Ashing will therefore be accompanied by an increase in the efficiency of detection. This is shown in Table III.

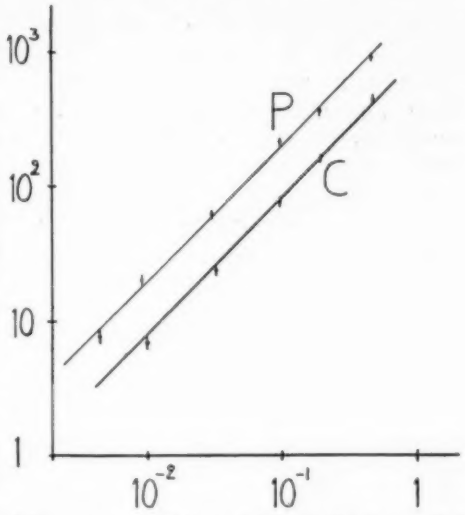

Diagram 4. Relation between the concentration of beryllium in human plasma (P) and red blood cells (C) in per cent (abscissa) and the number of counts per minute recorded (ordinate). Logarithmic scale on both coordinate axes.

5. Detection limit. The effective range of Po^{210} alphas in pure beryllium is about $5 \cdot 10^{-3}$ g/cm². Pure beryllium gives a maximum count of about $2 \cdot 10^4$ counts per min. with the present experimental arrangement. If 20 counts per minute are accepted as the detection limit, this corresponds to $5 \cdot 10^{-3} \cdot 20/2 \cdot 10^4 = 5 \cdot 10^{-6}$ g of beryllium as a theoretical detection limit. The practical detection limit is higher because the biologic samples always contain atoms other than beryllium atoms, thus reducing the probability of nuclear reactions with beryllium nuclei in the sample.

Table II

Relation between counting rate and approximate amount of dry substance for various organs of the rabbit

Organ	Counts per min.	Approximate percentage of dry substance	Product 10^{-2}
Blood serum	256 ± 8	9	23
Brain	150 ± 6	22	33
Liver	134 ± 6	29	39
Red blood cells	75 ± 5	36	27

Table III

Percentage of beryllium in human blood cells	Counts per min. on dried material	Counts per min. on ashed material	Quotient
0.3	21 ± 4	118 ± 7	5.7 ± 1.2
1.0	80 ± 6	328 ± 11	4.1 ± 0.5

Discussion

It seems quite clear that the recording of the 4.4 MeV gamma rays from the nuclear reaction Be^{9} $(a, n\ \gamma)C^{12}$ forms a possibility of detecting beryllium in biologic samples. As indicated by Diagr. 4, concentrations down to 10^{-3} per cent in serum might be detected without ashing, and a four- or fivefold increase can be achieved by ashing. Still better improvement can probably be reached with chemical enrichment of beryllium but this has not been tried in this work.

A considerable increase of sensitivity will probably be reached if a more intense alpha source, *e. g.* a cyclotron or a Van-de-Graaf generator is used. Due to the more intense beam, a factor of 10^{4} in sensitivity does not seem unreasonable. In that case, the nuclear reaction analysis of beryllium will probably be superior to the spectrographic method with which it has been possible to detect 10^{-8} g of beryllium in biologic material with 10 per cent accuracy (SMITH, BOYLE, FREDRICK and ZAK 1952).

If, when detecting beryllium in the way proposed, some doubt should arise that other substances are causing the gamma ray yield, the pulse spectrum should always be recorded as a rough control.

SUMMARY

The gamma rays of 4.4 MeV arising when beryllium is bombarded with alpha particles were used for the detection of beryllium in various known concentrations in blood plasma, red blood cells and other tissues. The presence of boron, aluminum, magnesium and other elements disturb the reaction. Various other factors influencing the analysis of beryllium in this way are discussed.

ZUSAMMENFASSUNG

Die Gammastrahlen von 4.4 MeV, welche bei der Bombardierung von Beryllium mit Alfateilchen entstehen, wurden für die Analyse von Beryllium in verschiedenen bekannten Konzentrationen verwendet. Blutplasma, rote Blutkörperchen und andere Gewebe wurden untersucht. Das Vorkommen von Bor, Aluminium, Magnesium und anderen Elementen macht die Kernreaktion unspezifisch. Andere Faktoren, welche die Analyse von Beryllium in dieser Weise beeinflussigen, werden diskutiert.

RÉSUMÉ

On a utilisé le rayonnement gamma (4.4 MeV) émis par du béryllium bombardé par des particules alpha pour détecter ce corps contenu à des taux connus dans du plasma sanguin, des globules rouges et d'autres tissus. La présence de bore, d'aluminium, de magnésium et d'autres corps perturbe la réaction nucléaire spécifique. Les auteurs discutent d'autres facteurs qui ont une influence sur la recherche du béryllium.

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AUS DER UNIVERSITÄTSFRAUENKLINIK (DIRECTOR: PROF. DR. MED. W. BICKENBACH), TÜBINGEN, DEUTSCHLAND

STRAHLENSCHUTZ DURCH ENTFERNUNG VON ZELLTOXINEN MIT KOLLIDON

(Polyvinylpyrrolidon)

von

Hans Burger und *Karl Peters*

Energiereiche Strahlen rufen im Organismus am Ort der Bestrahlung charakteristische Zellschäden hervor. Es gibt zunehmend Beweise dafür, dass die den Zellkern betreffenden Schädigungen zum Teil durch toxische Substanzen verursacht werden, die unmittelbar nach der Bestrahlung im Cyto- bzw. Karyoplasma entstehen. Unter ihrem Einfluss kommt es, wahrscheinlich durch Fermentinaktivierung, zu allgemeinen Funktionsstörungen der Zelle. Die Beeinflussung des Zellteilungsablaufs sowie chromosomale Veränderungen sind die morphologisch sichtbaren Folgen. Durch klinische Beobachtungen und experimentelle Untersuchungen ist erwiesen, dass eine lokalisierte Bestrahlung aber auch Auswirkungen auf den Gesamtorganismus hat. Es müssen also toxische, sekundär entstandene Bestrahlungsprodukte an das Blut abgegeben werden und über den eigentlichen Strahlenbereich hinaus zur Wirkung gelangen.

Seit der Beobachtung von PATT und Mitarbeitern, dass durch Verabreichung geeigneter Substanzen die durch Strahlentoxine hervorgerufenen Schäden verhindert oder abgeschwächt werden können, hat die Frage eines aktiven Strahlenschutzes sowohl aus praktischen Gründen als auch im Hinblick auf unsere Vorstellungen über den Mechanismus der biologischen Strahlenwirkung zunehmend Interesse gefunden. Es sind heute schon eine Reihe von Stoffen bekannt, die einen Strahlenschutz auszuüben vermögen. Ihre Wirkung beruht im allgemeinen auf einer Aktivierung humoraler Abwehrvorgänge, auf der Inaktivierung giftiger Spaltprodukte, vor allem des Wassers, und auf einer reversiblen Komplexbildung mit Fermentsystemen, die gegenüber den Strahlenprodukten empfindlich sind.

Bei der Red. am 26. VII 1953 eingegangen.

Die Beobachtungen von R. SCHUBERT, dass der kolloidale Bestandteil des Periston N, das *Kollidon*, zahlreiche pharmakologische Gifte und Toxine an sich bindet und über die Niere eliminiert, wiesen uns einen neuen Weg zur Verminderung der verschiedensten durch Strahlengifte hervorgerufenen Schäden. Mit der Anwendung von Periston N schien uns die Möglichkeit gegeben, eine Eliminierung der Strahlentoxine und damit eine Erholung des Organismus herbeizuführen. Bei Tierversuchen an röntgenganzbestrahlten Ratten konnten wir zeigen (BURGER und LEHMANN), dass das Kollidon imstande ist, auch die bei der Bestrahlung enstehenden Toxine über die Niere zur Ausscheidung zu bringen und damit eine Herabsetzung der Letalität bestrahlter Ratten herbeizuführen.

Die Beobachtung von SCHUBERT und WERNER, dass bereits in der Zelle gespeicherter Farbstoff durch Kollidonverabreichung wieder entfernt werden kann, veranlasste uns nunmehr zu prüfen, ob die Entgiftungswirkung des Kollidons bei der Bestrahlung nur *interzellulär* oder aber auch *intrazellulär* zur Auswirkung kommt.

Material und Methode

Für die Untersuchung der Wirkung von Kollidon auf die Zelle erschien uns die Bohne *Vicia faba equina* besonders geeignet. Es wurde genetisch reines Saatgut verwendet, welches freundlicherweise vom Institut für Pflanzenbau und Pflanzenzüchtung an der landwirtschaftlichen Hochschule Stuttgart/Hohenheim zur Verfügung gestellt wurde. Um die Wirkung von Kollidon auf die pflanzliche Zelle untersuchen zu können, war es erforderlich, das Kollidon in eine den pflanzlichen Ansprüchen genügende Nährlösung zu bringen. So wurden zunächst 6 g Kollidon in 100 ccm der Nährlösung nach von der Crone gelöst, entsprechend der gebräuchlichen Konzentration im Periston N. Die Auszählung der Mitosen nach 19-stündiger Einwirkungszeit ergab einen völligen Stillstand der Zellteilungen. Aus diesem Grund wurde die Konzentration des Kollidons auf 3 % vermindert. Bei dieser Konzentration hat Kollidon keine toxische Wirkung auf die pflanzliche Zelle. Um nun einen intrazellulären Schaden hervorzurufen, wurden die Wurzelspitzen mit Radium (50 r, 5 r/min.) bestrahlt. In den Vorversuchen wurde festgestellt, dass die Zahl der Mitosen unter denjenigen Werten nach alleiniger Radiumeinwirkung lag, wenn Kollidon nach der Bestrahlung zur Anwendung kam. Wurde mit der Kollidonbehandlung bereits 12 Stunden vor der Bestrahlung begonnen und wurden die Wurzelspitzen dann nach der Bestrahlung über die ganze Versuchszeit in einer kollidonhaltigen Lösung belassen, dann lagen die Mitosewerte ebenfalls unterhalb der Häufigkeit nach alleiniger Radiumwirkung. Nur die Versuchsreihen zeigten ein positives Ergebnis, bei denen mit der Kollidoneinwirkung 12 Stunden vor der Bestrahlung begonnen wurde und bei denen die Bohnen dann in eine kollidonfreie Nährlösung gebracht wurden. Dadurch wurde das für eine Ausschwemmung des Kollidons aus der Zelle erforderliche Konzentrationsgefälle erreicht. Es bestand nunmehr die Möglichkeit festzustellen, ob das Kollidon toxische Bestrahlungsprodukte bei der Ausschwemmung aus der Zelle bindet und mitnimmt.

Für die Versuche wurden jeweils 14—20 Bohnen bei 22° C. zur Ankeimung gebracht. Nach 4 Tagen wurden die Keimlinge verwendet, die eine Wurzellänge von 1.5 mm aufwiesen. Jeweils 6 Bohnen entsprechender Wurzellänge wurden ausgesucht, sodass nur Material von der gleichen Wachstumsmodifikation verwendet wurde. 3 Keimlinge

wurden für die Bestrahlung benutzt, während die anderen 3 als Kontrolle dienten. Hinsichtlich der Bestrahlungstechnik sei auf eine frühere Veröffentlichung verwiesen (PETERS), in der die Bestrahlungsapparatur abgebildet und die Methode eingehend beschrieben wurde. Die Bestrahlung wurde mit jeweils 3 Radiumstäbchen à 10 mg durchgeführt. Die Filterung pro Stäbchen betrug 0.55 Platinäquivalent. Eingestrahlt wurden jeweils 50 r, 5 r/min. In Abständen von 0, 2, 4, 7, 12, 18, 24 und 30 Stunden wurden die Wurzelspitzen in Flemmingscher Lösung fixiert. Für die cytologische Untersuchung wurde die Nuklealquetschmethode nach HEITZ zur Anwendung gebracht. Von jeder Wurzelspitze wurden 4 Quetschpräparate hergestellt. Aus jedem Präparat wurden 20 Gesichtsfelder der meristematischen Zone ausgezählt (Ok. 10+, Objekt. A = 1.30), und die darin enthaltenen Mitosen und Interphasenzellen statistisch erfasst. Strahlenschädigungen an den Chromosomen bzw. Chromatiden in der Ana- und Telophase, wie Chromosomenbrüche, Chromosomenverklebungen und bewegungsunfähige Chromosomen wurden besonders registriert. Ebenfalls wurden die als Folge dieser Schädigungen in den Zellen auftretenden Nebenkerne erfasst. Den Ergebnissen liegen 130,000 Zellen und davon 14,500 Mitosen zugrunde, sodass die Ergebnisse in jedem Fixierungspunkt aus ca. 450 Mitosen gewonnen wurden.

Versuchsergebnisse

Die Mitosehäufigkeitsverteilung in Diagramm 1 zeigt, dass eine 3 % Lösung von Kollidon ohne Einfluss auf die Mitosehäufigkeit im Vergleich zu den Kontrollen ist. Unter der Einstrahlung von Radium kommt es zu einer charakteristischen Verminderung der Mitosehäufigkeit. Bis zu 7 Stunden nach der Bestrahlung ist zwischen der Mitosehäufigkeitsverteilung nach alleiniger Radiumeinwirkung und nach Radiumbestrahlung mit 12-stündiger Vorbehandlung mit Kollidon kein Unterschied zu

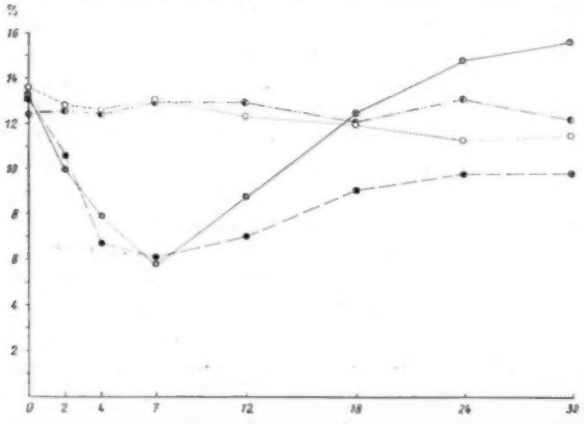

Diagramm 1. Häufigkeitsverteilung der Mitosen in dem Wurzelspitzenmeristem von *Vicia faba equina*. (○ · · · · ○) Kontrollen; (◐- · · · -◐) Kollidon 3 g/100 ccm Nährlösung; (●- - -●) Radium 50 r, 5 r/min.; (○——○) Radium + Kollidon (12St vorher). Ordinate: Zahl der Mitosen in % der Zellen. Abszisse: Fixierungszeiten in Stunden. Koordinatenschnittpunkt: Endpunkt der Bestrahlung.

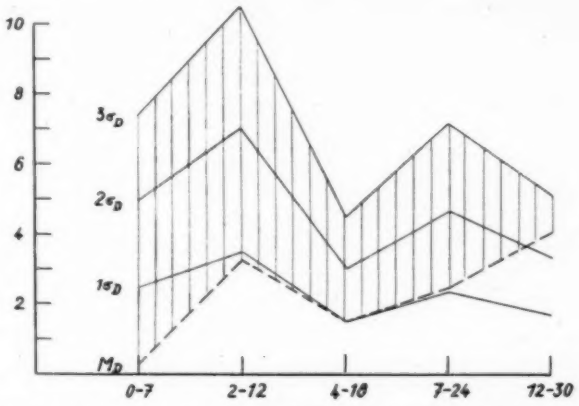

Diagramm 2. Graphische Darstellung der Differenz der Mittelwerte der Mitosehäufigkeiten (M_D) und der Differenz der 1, 2 und 3-fachen Streuung (σ_D) gewonnen aus gleitenden Mittelwertskollektiven bestehend aus jeweils 4 Fixierungspunkten.

beobachten. Nach 12 Stunden ist ein geringer Unterschied vorhanden. Der Wert der unbestrahlten Kontrollen wird nach 18 Stunden erreicht und nach 24 und 30 Stunden sogar überschritten. Demgegenüber bleibt die Mitosehäufigkeitsverteilung nach alleiniger Radiumeinwirkung auch noch nach 30 Stunden unterhalb des Werts der Kontrollen. Aus dem Verlauf der Kurve ist ersichtlich, dass zunächst einmal Kollidon in der Zelle vorhanden ist. Zum anderen zeigt der Verlauf der Kurve, dass das Kollidon eine gewisse Zeit benötigt, um aus der pflanzlichen Zelle herauszudiffundieren. Das Ansteigen der Mitosehäufigkeit in den kollidonbehandelten, bestrahlten Wurzeln über die Kontrollen lässt erkennen, dass das Kollidon mitosehemmende Stoffe bindet und bei seinem Austritt aus der Zelle in die kollidonfreie Nährlösung mitnimmt, d. h. Kollidon führt zu einer Entgiftung der Zelle von toxischen, sekundären Bestrahlungsprodukten. Um festzustellen, ob diese Unterschiede statistisch zu sichern sind, wurden die Differenzen der Mittelwerte und der mittleren Streuung von gleitenden Kollektiven (jeweils 4 Messwerte) gebildet. Im Diagrame 2 sind die Gruppenkollektivwerte dargestellt. Aus dem Verlauf der Kurve der Differenz der Mittelwerte (M_D) und derjenigen der dreifachen mittleren Streuung (σ_D) ist die Tendenz ersichtlich, dass im letzten Kollektiv (12—30 Stunden) bereits eine 2-fache statistische Sicherung überschritten und eine 3-fache Sicherung angestrebt wird. Nimmt man die Differenz der Mittelwerte und der 3-fachen mittleren Streuung des 30-Stundenwertes allein, so ist der Unterschied zwischen der Radiumreihe und der bestrahlten Kollidonreihe statistisch gesichert.

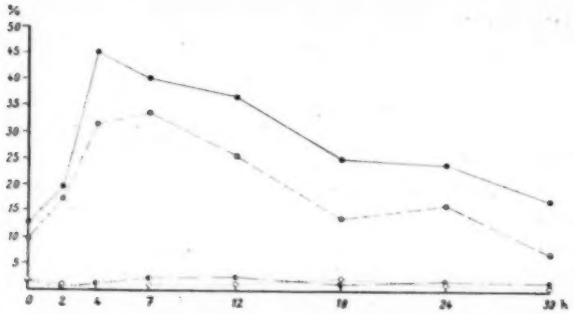

Diagramm 3. Häufigkeitsverteilung der pathologischen Ana- und Telophasen in den Wurzelspitzenzellen von *Vicia faba equina*. (○ · · · · ○) Kontrollen; (◐ · · · · ◐) Kollidon 3 g/100 ccm Nährlösung; (●——●) Radium 50 r, 5 r/min.; (○ – – – ○) Radium + Kollidon. Ordinate: Zahl der path. Ana- und Telophasen in Prozent der normalen Ana- und Telophasen. Abszisse: Fixierungszeiten in Stunden. Koordinatenschnittpunkt: Endpunkt der Bestrahlung.

Die Differenz der Mittelwerte beträgt $M = 5.9$ und die Differenz der Streuung $t \times \sigma_D = 3xo$, $71 = 2.34$ also $M_D > t \times \sigma_D$ (unter Zugrundelegung einer Sicherungsgrenze von $P = 0.27$ %).

Da die Steigerung der Mitosehäufigkeit nach Radium- und Kollidonbehandlung eine Entgiftung der Zellen erkennen lässt, war es umso interessanter festzustellen, ob auch die Chromosomenbrüche und Chromosomenverklebungen durch diesen Effekt beeinflusst werden. Im Diagrame 3 sind die Häufigkeitsverteilungen der pathologischen Ana-und Telophasen erfasst. Die Beobachtungspunkte 0 und 2 Stunden nach der Bestrahlung lassen noch keine Unterschiede zwischen der Radiumreihe und der Radium-Kollidonreihe erkennen. Nach 4 Stunden liegt die Häufigkeit der pathologischen Ana- und Telophasen der Radium-Kollidonreihe bereits unterhalb derer, die nach alleiniger Radiumeinwirkung erhalten wurde. Diese Verminderung bleibt dann während des ganzen Versuches bestehen. Auch in dem Vorkommen der pathologischen Ana- und Telophasen besteht zwischen der Kontrollreihe und der kollidonbehandelten Serie, die nicht bestrahlt wurde, kein Unterschied, was für die völlige Ungiftigkeit von Kollidon in der verwendeten Konzentration spricht. Die statistische Berechnung aus den Variationskurven der pathologischen Ana- und Telophasen nach der Radiumeinwirkung und nach der Radiumbestrahlung bei vorheriger Kollidonverabreichung ist im Diagrame 4 graphisch dargestellt. Ebenso wie beim Verlauf der Mitosen (Diagramm 2) ist auch hier mit zunehmendem Abstand vom Bestrahlungszeitpunkt die Tendenz zu einer 3-fachen statistischen Sicherung vorhanden. Der 30-Stundenwert allein lässt sich ebenfalls statistisch sichern, da die Dif-

ferenz der Mittelwerte $M_D = 10.34$ grösser ist als das Produkt aus $t \times \sigma_D = 3.3 \times 2.7 = 8.8$ unter Zugrundelegung einer Sicherungsgrenze von $P = 0.27$ %.

Die als Folge von Chromosomenbrüchen und zum Teil von Chromosomenverklebungen und bewegungsunfähigen Chromosomen in den Zellen nach der Beendigung der Zellteilung auftretenden Kleinst- und Nebenkerne wurden ebenfalls statistisch erfasst (Diagramm 5). In Übereinstimmung mit dem Verlauf der Variationskurven der pathologischen Ana- und Telophasen (Diagramm 3) ist auch hier die Variationskurve der Nebenkerne der bestrahlten kollidonbehandelten Zellen niedriger als die, welche nach alleiniger Radiumbestrahlung erhalten wurde. Damit wird der Befund bestätigt, dass die Zahl der pathologischen Ana- und Telophasen unter Kollidonbehandlung vermindert ist. Da die an den Nebenkernen gewonnenen Ergebnisse immer zeitlich hinter den Befunden der pathologischen Ana- und Telophasen liegen, ist aus dem Verlauf der Darstellung der statistischen Sicherung (Diagramm 6) nur eine geringe Tendenz zur Sicherung zu erkennen. Im letzten Kollektiv (12—30 Stunden) wird erst die $1\sigma_D$-Grenze von der M_D-Linie überschritten. Der 30-Stundenwert allein genommen bestätigt aber auch hier die angedeutete Tendenz zur statistischen Sicherung, da sich diese Werte sichern lassen. Die Differenz der Mittelwerte $M_D = 47$ ist grösser als $t \times \sigma_D = 3 \times 12.7 = 44.7$ unter Zugrundelegung einer Sicherungsgrenze von $P = 0.27$ %.

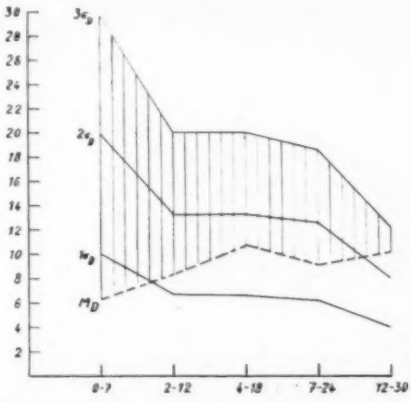

Diagramm 4. Darstellung der Differenz der Mittelwerte der path. Ana- und Telophasen (M_D) und der Differenz der 1, 2 und 3-fachen Streuung (σ_D) gewonnen aus dem gleitenden Mittelwertskollektiven bestehend aus jeweils 4 Fixierungspunkten.

In Übereinstimmung mit den Befunden der pathologischen Ana- und Telophasen ist auch bei den Nebenkernen ein Unterschied zwischen den unbestrahlten Kontrollen und den allein mit Kollidon behandelten Zellen nicht vorhanden.

Diskussion

Zur Beurteilung des intrazellulären Strahleneffektes unter Kollidonbehandlung wurden von uns 3 Kriterien, die Mitosehäufigkeit, die Anzahl der pathologischen Ana- und Telophasen und das Auftreten von Nebenkernen herangezogen, die übereinstimmend eine Herabsetzung des zellulären Strahlenschadens durch das Kollidon ergeben haben. Damit ist

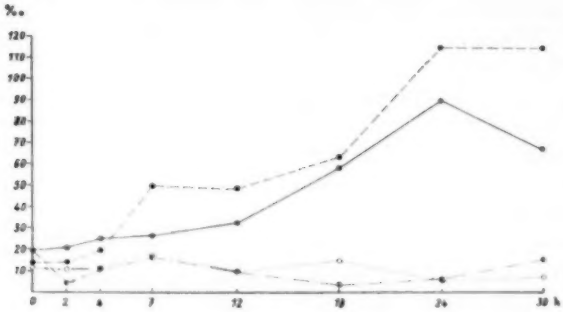

Diagramm 5. Häufigkeitsverteilung der Nebenkerne in den Wurzelspitzenzellen von *Vicia faba equina*. (○ · · · · ○) Kontrollen; (◐- · · · -◐) Kollidon 3 g/100 ccm Nährlösung; (● - - - ●) Radium 50 r, 5 r/min.; (○——○) Radium + Kollidon (12St vorher). Ordinate: Zahl der Zellen mit Nebenkernen in % der gesamten Zellzahl. Abszisse: Fixierungszeiten in Stunden. Koordinatenschnittpunkt: Endpunkt der Bestrahlung.

der Nachweis erbracht, dass das Kollidon intrazellulär wirkt und einen Strahlenschutz auszuüben vermag. Bei der Frage nach dem Wirkungscharakter des Kollidons, das zahlreiche Eigenschaften mit den Serumeiweisskörpern gemeinsam hat, interessiert vor allem die Feststellung von Forssberg, dass die Strahlenempfindlichkeit der verschiedensten zellulären Fermentsysteme bei Anwesenheit eiweissähnlicher Substanzen wesentlich herabgesetzt ist. Es spricht wenig für diese Art des Wirkungsmechanismus, da bei längerem Verbleiben des Kollidons in der bestrahlten Zelle eine zunehmende Mitosehemmung eintritt. Diese Beobachtung erscheint uns aus 3 Gründen wichtig, zeigt sie doch, dass das Kollidon von der Pflanzenzelle zwar aufgenommen, aber nicht ohne weiteres wieder abgegeben wird, dass die Zelltoxine durch das Kollidon intrazellulär gebunden und festgehalten werden und schliesslich, dass diese Bindung nicht an der toxophoren Gruppe der Zellgifte erfolgt, da die Toxine ja weiterhin wirksam bleiben. Durch eine Variation der Versuchsanordnung konnten wir zeigen, dass der Entgiftungseffekt des Kollidons dann eintritt, wenn es gelingt, das toxinbeladene Kollidon aus der Zelle durch Herstellen eines Konzentrationsgefälles zu eliminieren. Gleichzeitig wurde damit der Nachweis erbracht, dass ein Teil der Strahlenschäden und was besonders beachtenswert ist, ein gewisser Anteil der Chromosomenschäden, auf der Wirkung von Zelltoxinen beruht, die auch noch nach 30 Stunden Wirkungen erkennen lassen. Mit der Anwendung von Kollidon ergibt sich somit innerhalb gewisser Grenzen die Möglichkeit zu beurteilen, welcher Anteil der Chromosomenschäden direkt auf das Trefferereignis zu beziehen und damit irreversibel ist und

welcher Anteil auf toxischen, sekundär entstandenen Bestrahlungsprodukten beruht.

Da der Wirkungscharakter der bisher bekannten Strahlenschutzstoffe von dem des Kollidons grundsätzlich verschieden ist, ergeben sich aus unseren Untersuchungen neue Gesichtspunkte für das Verständnis der biologischen Strahlenwirkung. Ebenso möchten wir glauben, dass die mitgeteilten Befunde, die frühere Ergebnisse mit Periston N bestätigen, unter besonderen Umständen grosse praktische Bedeutung erlangen können, zeigt doch das Periston N bei therapeutischen Bestrahlungen erfreuliche Wirkungen als Katermittel. Ob jedoch seiner Anwendung bei der Bestrahlung Carcinomkranker infolge seiner strahlenschützenden Wirkung Schranken gesetzt sind, werden weitere Versuche entscheiden müssen.

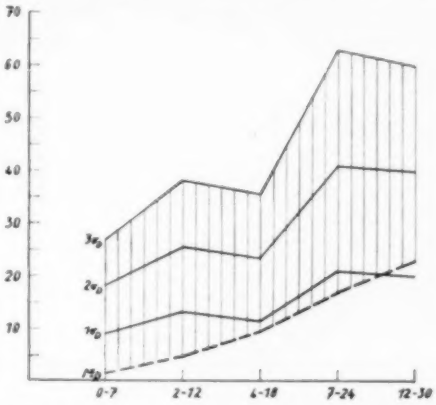

Diagramm 6. Darstellung der Differenz der Mittelwerte der Nebenkerne (M_D) und der Differenz der 1, 2 und 3-fachen Streuung (σ_D) gewonnen aus gleitenden Mittelwertskollektiven, bestehend aus jeweils 4 Fixierungspunkten.

ZUSAMMENFASSUNG

Die an Wurzelkeimlingen der Bohne *Vicia faba* hervorgerufenen Strahlenschäden werden durch Kollidon deutlich abgeschwächt. Nach Kollidonbehandlung beobachtet man eine Normalisierung der Mitosetätigkeit, eine Verminderung der pathologischen Ana- und Telophasen und als Folge davon eine Herabsetzung der Zahl der Nebenkerne. Die Wirkung des Kollidons beruht auf seiner Fähigkeit, die in der Zelle nach der Bestrahlung auftretenden Zelltoxine zu binden und sie bei seinem Austritt aus der Zelle mitzunehmen.

SUMMARY

Irradiation damage to the germinating roots of *Vicia faba* is less after the application of collodion since mitosis becomes more normal. Pathologic anaphases and telophases are reduced, in consequence of which there are fewer paranuclei. The effect of collodion is due to its power to fix the cell toxin present in the cell after irradiation and carry it away from the cell.

RÉSUMÉ

Les radiolésions des racines de *Vicia faba* en germination sont moins intenses après application de collodion, étant donné que la mitose devient plus normale. Les anaphases et télophases pathologiques sont moins nombreuses, d'où un moins grand nombre de paranucléi. L'effet du collodion est dû à son aptitude à fixer la toxine cellulaire présente dans la cellule après irradiation et à l'éloigner de la cellule.

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